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(54) Title: COMPOSITION AND METHOD FOR PREVENTION AND TREATMENT OF CARDIOPULMONARY AND RENAL FAILURE OR DAMAGE ASSOCIATED WITH ISCHEMIA, ENDOTOXIN RELEASE, ARDS OR BROUGHT ABOUT BY ADMINISTRATION OF CERTAIN DRUGS

(57) Abstract

A pharmaceutical composition comprises an agent such as an adenosine A2a agonist agent and/or nucleic acid comprising an oligonucleotide(oligo) that is anti-sense to an adenosine A1, A2a, A2b or A3 receptor gene, mRNA, flanking regions or regions bridging the intro/exon borders, which oligos are effective to prevent, alleviate or inhibit adenosine-mediated cardiac, pulmonary and/or renal functional difficulties, damage or failure, such as those observed in diseases and conditions such as ARDS, hypoxia, etc. or associated with the administration of therapeutic and diagnostic agents such as adenosine cysplatin, metal ion-containing agents, etc., mixtures thereof, and optionally a surfactant, a carrier and other therapeutic and diagnostic agents and other formulation components. The composition is provided in the form of various formulations that are, for example, effective for preventing or alleviating bronchoconstriction, allergy and/or inflammation associated with ARDS, RDS, etc., deleterious side effects observed upon treatment of SVT patients, upon administration of cardiac stress tests or imaging tests, etc.

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COMPOSITION & METHOD FOR PREVENTION & TREATMENT OF CARDIOPULMONARY & RENAL FAILURE OR DAMAGE ASSOCIATEDWITH ISCHEMIA, ENDOTOXIN RELEASE, ARDS OR BROUGHT ABOUT BY ADMINISTRATION OF CERTAIN DRUGS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a composition, formulations and method for prevention and therapy of cardiac, cardiopulmonary and renal damage or failure seen in certain diseases or conditions associated with ischemia and/or endotoxin release, acute respiratory distress syndrome (ARDS), or brought about by administration of certain drugs such as cancer chemotherapeutic agents, glycerol, radiocontrast media, and adenosine which is administered, for example, in stress tests and the treatment of supraventricular tachycardia (SVT).

Description of the Background

Adenosine, a natural nucleoside, may constitute an important natural mediator of many of diseases, including asthma, and the like. The inhalation of adenosine by asthmatics, but not by normal subjects, causes broncho-constriction. Theophylline, a xanthine, may be useful in reversing this asthmatic effect. Other experimental data suggest the possibility that adenosine receptors may also be involved in allergic and inflammatory responses. It has been postulated that the modulation of signal transduction at the surface of inflammatory cells influences acute inflammation. Adenosine is said to inhibit the production of super-oxide by stimulated neutrophils. Moreover, the treatment of experimental allergic uveitis produced a marked reduction in inflammation. Adenosine may attenuate this behavior by reducing the hyperactivity of the central dopaminergic system.

Adenosine plays a unique role in the body as a regulator of cellular metabolism. It can raise the cellular level of AMP, ADP and ATP which are the energy intermediates of the cell. Adenosine can stimulate or down regulate the activity of adenylate cyclase and hence regulate cAMP levels. CAMP, in turn, plays a role in neurotransmitter release, cellular division and hormone release. Adenosine's major role appears to be to act as a protective injury autocoid. In any condition in which ischemia, low oxygen tension or trauma occurs adenosine appears to play a role. Defects in synthesis, release, action and/or degradation of adenosine have been postulated to contribute to the over activity of the brain excitatory amino acid neurotransmitters, and hence various pathological states. Recent evidence suggests that adenosine may also play a protective role in stroke, CNS trauma, epilepsy, ischemic heart disease, coronary by-pass, radiation exposure and inflammation.

Overall, adenosine appears to regulate cellular metabolism through ATP, to act as a carrier for methionine, to decrease cellular oxygen demand and to protect cells from ischemic injury. Adenosine is a tissue hormone or inter-cellular messenger that is released when cells are subject to ischemia, hypoxia, cellular stress, and increased workload, and or when the demand for ATP exceeds its supply. Adenosine is a purine and its formation is directly linked to ATP catabolism. It appears to modulate an array of physiological processes including vascular tone, hormone action, neural function, platelet aggregation and lymphocyte differentiation. It also may play a role in DNA formation, ATP biosynthesis and general intermediary metabolism. It is suggested that it regulates the formation of cAMP in the brain and in a variety of peripheral tissues. Adenosine is also said to participate in the auto-regulation of blood flow in

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the heart, brain, skeletal muscle, adipose tissue and kidney. In the kidney, for example, it may act as a vasoconstrictor, but as a vasodilator in each of the other vascular beds. Adenosine is said to antagonize the catabolic effects of hormones and promote the action of the anabolic hormone insulin. In addition, adenosine may also act to attenuate the release of neurotransmitters in both the central and peripheral nervous systems, inhibit the secretion of insulin and prevent platelet aggregation. Adenosine has been said to modulate the function of T lymphocytes by a mechanism which involves the regulation of protein synthesis. Adenosine regulates cAMP formation through two receptors A_1 and A_2 . Via A_1 receptors, adenosine reduces adenylate cyclase activity, while it stimulates adenylate cyclase at A_2 receptors. The adenosine A_1 receptors are more sensitive to adenosine than the A_2 receptors. The CNS effects of adenosine are generally believed to be A_1 -receptor mediated, where as the peripheral effects such as hypotension, bradycardia, are said to be A_2 receptor mediated.

Adenosine is said to modulate adenylate cyclase activity as well as nerve cell firing and the release of neurotransmitters such as aspartate, glutamate, GABA and serotonin. It has sedative and anti-convulsive properties and is said to inhibit both spontaneous and evoked nerve firing. Its action is antagonized by caffeine and theophylline. Adenosine's action is mediated through cell surface receptors called A_1 , A_{2a} , A_{2b} and A_3 , and it acts as a purinergic inhibitory neuro or cellular transmitter. Adenosine also has been implicated in anxiety, analgesia, sleep and depression, in modifying CNS alertness, acting as neuro-modulator, which actions are terminated by cellular uptake or deamination. It also has been said to potentiate the effects of histamine, reduce neuronal excitability, and to exert the majority of its central effects pre-synaptically by inhibition of calcium-dependent neurotransmitter release.

It has been also suggested than the production and release of adenosine is closely linked to energy balance. During ischemia, adenosine levels accumulate and ATP is rapidly depleted. It appears to be released at the site of trauma or when the cellular oxygen supply is reduced by hypoxia or ischemia and, thus, dampens cellular activity and increases blood flow via vascular dilation. A localized increase of adenosine at traumatic foci plays an important homeostatic role by down-regulating physiological function and, thereby, conserving ATP. In almost every organ ischemia induces an elevation of adenosine levels, which results in a slowing of that organ's function, a process which is postulated to be mediated by adenosine receptors. In recognition of this, adenosine has been termed a "retaliatory metabolite" and an endogenous neuro-protective agent. Adenosine, therefore, appears to play overall a homeostatic role throughout the body or, in a sense, to generate recovery time for traumatized tissue.

Adenosine has been implicated in the regulation of coronary blood flow and said to have negative chromotropic and inotrophic effects on heart contractibility. These effects may be mediated directly via adenosine receptors, or indirectly by either inhibition of the release of other neurotransmitters or by antagonism of the myocardial action of noradrenalin. Adenosine injections have been used for the treatment of supraventricular tachycardia (SVT). During hypoxia, ischemia or reactive hyperaemia, adenosine appears to be freely released and, through its action reduce cellular hypoxic stress by slowing cellular metabolism. Thus, it appears to act as an anti-injury autocoid. It is believed that both morbidity and mortality from acute coronary artery occlusion may be reduced if local myocardial adenosine concentration is augmented. Adenosine is said to increase collateral coronary circulation and even inhibit the generation of superoxide anions by granulocytes, thus reducing vascular endothelial

damage. Another effect of adenosine appears to be to block granulocyte activation, and thereby reduce capillary plugging and the "no-reflow" phenomenon which contributes to post-stroke neuro-degeneration.

Adenosine and a majority of adenosine mononucleotides have been said to also possess radioprotective activity. This protective activity is thought to occur through A₁ receptors. Internal kidney vasoconstriction, however, has been observed upon the administration of radiocontrast agents for imaging purposes. Adenosine, calcium and ischemia have been postulated to have a role in this radiocontrast agent-induced intra-renal vasoconstriction. Ischemia or oxygen derivation in many instances are said to produce kidney damage. Certain cancer chemotherapeutic agents, such as cisplatin and methotrexate, as well as glycerol and the administration of metal ions such as thallium (Th), lead (Pb) and cadmium (Cd) have also been associated with kidney damage, which may become extensive upon the release of endotoxins, and even culminate in sepsis. Known adenosine receptor antagonists have been said to attenuate the thus produced renal damage. Adenosine, thus, may have a role as a natural mediator of intra-renal vasocontriction. In particular, the kidney has a significant number of adenosine receptors, adenosine's effect on the kidneys could be mediated primarily through the stimulation of adenosine receptors.

One of the characteristics of hyper-responsive subjects in particular is the over-expression of the adenosine A₁ receptor. When activated by adenosine, whose levels are induced, for example, by ischemia or by certain agents such as glycerol, endotoxin, chemotherapeutic agents such as cisplatin and methotrexate, and by radiocontrast media, the adenosine A₁ receptor may cause life threatening, even fatal, renal damage. Adenosine receptor antagonists, such as theophylline, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX), are known to counter adenosine-mediated bronchoconstriction in asthmatics. Theophylline has been also employed to prevent a reduction in the glomerular filtration rate observed upon administration of a radiocontrast medium. The therapeutic potential, however, of currently available adenosine A₁ receptor-specific antagonists is drastically limited by their toxicity. Theophylline, for example, frequently results in significant toxicity because of its narrow therapeutic dose range. The availability of an alternative strategy to prevent and treat the adenosine associated renal dysfunction, damage and failure observed in patients with hypoxia or ischemia, and upon the administration of certain drugs, particularly in hyperresponsive individuals, would clearly be of extreme prophylactic and therapeutic value.

Adenosine A₁-mediated diseases and conditions, such as asthma, allergic rhinitis, and Acute Respiratory Distress Syndrome (ARDS), including in pregnant mothers, and RDS in premature born infants, among others, are common diseases in industrialized countries, and in the United States alone account for extremely high health care costs. These diseases or conditions have recently been increasing at an alarming rate, both in terms of prevalence, morbidity and mortality. In spite of this, their underlying causes still remain poorly understood. Acute Respiratory Distress Syndrome (ARDS) is also known in the medical literature as stiff lung, shock lung, pump lung and congestive atelectasis, and its incidence is 1 out of 100,000 people. ARDS is believed to be caused by a failure of the respiratory system characterized by fluid accumulation within the lung which, in turn, causes the lung to stiffen. The condition is triggered by a variety of processes that injure the lungs. In general ARDS occurs as a medical emergency. It may be caused by a variety of conditions that directly or indirectly cause the blood

vessels to "leak" fluid into the lungs. In ARDS, the ability of the lungs to expand is severely decreased and damage to the air sacs and lining (endothelium) of the lung is extensive. The concentration of oxygen in the blood remains very low in spite of high concentrations of supplemental oxygen which are generally administered to a patient. Among the systemic causes of lung injury are trauma, head injury, shock, sepsis, multiple blood transfusions and medications. Pulmonary causes include pulmonary embolism, severe pneumonia, smoke inhalation, radiation, high altitude, near drowning, and more. ARDS symptoms usually develop within 24 to 48 hours of the occurrence of an injury or illness. It is believed that cigarette smoking may be a risk factor.

Among the most common symptoms of ARDS are labored, rapid breathing, nasal flaring, cyanosis blue skin, lips and nails caused by lack of oxygen to the tissues, breathing difficulty, anxiety, stress and tension. Additional symptoms that may be associated with this disease are joint stiffness and pain and temporarily absent breathing. The diagnosis of ARDS is commonly done by testing for symptomatic signs. A simple chest auscultation or examination with a stethoscope, for example, will reveal abnormal breath sounds which are symptomatic of the condition. Confirmatory tests used in the diagnosis of ARDS include chest X-rays and the measurement of arterial blood gas. In some cases ARDS appears to be associated with other diseases, such as patients with acute myelogenous leukemia, who developed acute tumor lysis syndrome (ATLS) after treatment with cytosine arabinoside. In general, however, ARDS appears to be associated with traumatic injury, severe blood infections such as sepsis, or other systemic illness, the administration of high dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure, and in many cases death. In premature babies ("primies"), the lungs are not quite developed and, therefore, the fetus is in an anoxic state during development. In addition, lung surfactant is generally yet not present in sufficient amounts at this early stage of life. However, premies often hyper-express the adenosine A₁ receptor and/or underexpress the adenosine A2a receptor and are, therefore, susceptible to diseases and conditions such as bronchoconstriction, lung inflammation, and ARDS, among others. Respiratory distress syndrome (RDS) occurring in the preterm infant is an extremely serious problem. A primary cause of RDS in such preterm infants is the immature developmental stage of the infant, resulting in lack of surfactant, a material critical for normal respiration. Preterm infants exhibiting RDS are ventiliated, and administered oxygen and surfactant preparations. Infants with RDS, when they survive, frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease of early infancy. This too is often fatal.

The death rate from ARDS exceeds 50%. Although many survivors recover normal lung function, some individuals may suffer permanent lung damage, which ranges from mild to severe. Moreover, ARDS patients are often afflicted with complications, such as multiple organ system failures. Up to the present time, no measures to prevent or treat ARDS are known. Recently, however, it was reported that an increase in the ratio of certain fatty acid by-products of phosphatydic acid metabolism is predictive of the likelihood that a patient will develop ARDS and that, furthermore, the predictive value of the index correlates with the severity of the illness. Remedial treatment is limited to compensating for the severe dysfunction of the respiratory system and treating the underlying cause of the lung injury. One of the fastest developing symptoms in ARDS is hypoxia, which is generally treated by administration of hyperbaric oxygen, often at high concentrations, many times 100% oxygen concentrations are needed.

This is done in many circumstances by necessity by means of intubation or by passing a tube through the nose or the mouth of the patient into the trachea (airway). In addition, mechanical ventilation or a respirator, a machine used to aid the breathing, is usually necessary for further supporting the respiratory system. This treatment may need to be continued until a gradual weaning from the mechanism is tolerated. Although no therapeutic treatment of ARDS itself exists at the present time, other medications may be administered to treat infection, reduce inflammation and eliminate fluid within the lungs. The minimal daily chores become tremendously difficult to perform under the circumstances, and often the sole recommendation doctors can offer to ARDS patients is that they join support groups to share common experiences and problems with other ARDS victims. As already indicated, respiratory distress syndrome also occurs in premies and infants. Thus, in view of the potential for predicting whether or not a patient may develop ARDS, it becomes even more important to make available a novel strategy to treat Acute Respiratory Disorder Syndrome (ARDS), because now it has become possible to apply it to the prevention of ARDS as well, be it in adults, in children, or in prematurely born babies ("primies").

Adenosine, in addition, slows the conduction time through the heart's A-V node, may interrupt the reentry pathways through the A-V node, and may restore normal sinus rhythm in patients with paroxymal supraventricular tachycardia (PSVT), more commonly described as supraventricular tachycardia (SVT), including that associated with Wolff-Parkinson-White Syndrome. The systemic administration of adenosine was found useful for treating SVT, and as a pharmacologic means to evaluate cardiovascular health via an adenosine stress test commonly administered by hospitals and by doctors in private practice. Adenosine administered by inhalation is known to cause bronchoconstriction in asthmatics, possibly due to mast cell degranulation and histamine release, effects which have not been observed in normal subjects. Adenosine infusion has caused respiratory compromise in patients with obstructive pulmonary disease. As a consequence of the untoward side effects observed in many patients, caution is recommended in the prescription of adenosine to patients with a variety of conditions, including obstructive lung disease, emphysema, bronchitis, etc, and complete avoidance of its administration to patients with or prone to bronchoconstriction or bronchospasm, such as asthma. In addition, the administration of adenosine must be discontinued in any patient who develops severe respiratory difficulties.

Allergic rhinitis afflicts one in five Americans, accounting for an estimated \$4 billion in health care costs each year: \$2 billion for the seasonal variant and more than \$2 billion for the perennial variant. If associated airway diseases are considered, the cost may approach \$10 billion. But even this enormous figure may underestimate the disorder's true toll. Because many people mislabel their symptoms as persistent colds or sinus problems, allergic rhinitis is probably underdiagnosed. If other associated airway diseases are considered, the cost may approach \$10 billion. But even this enormous figure may underestimate the disorder's true toll. Because many people mislabel their symptoms as persistent colds or sinus problems, allergic rhinitis is probably underdiagnosed. Rhinitis can occur at any age. Typically, IgE combines with allergens in the nose to produce chemical mediators, induction of cellular processes, and neurogenic stimulation, causing an underlying inflammation. Symptoms include nasal congestion and discharge, sneezing, and itching. Sufferers also may have itchy, watery, swollen eyes. Over time, allergic rhinitis may predispose sufferers to the development of sinusitis, otitis media with effusion, and nasal polyposis. In addition, rhinitis can exacerbate asthma. Allergic rhinitis also can be associated with

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mood and cognitive disturbances, fatigue and irritability. Many medications may produce adverse reactions-such as sedation with some over-the-counter anti-histamines-that could further impair a patient's quality of life. An understanding of the pathophysiology of the nose will often dictate appropriate therapy. Cholinergic pathways, when stimulated, produce typical secretions that can be identified by their glandular constituents so as to implicate neurologic stimulation. Secretions typical of increased vascular permeability are found in allergic reactions as well as upper respiratory infections. Degranulation of mast cells results in the release of preformed mediators that interact with various cells, blood vessels, and mucous glands to produce the typical rhinitis symptoms. Most early- and late-phase reactions occur in the nose after allergen exposure. The late-phase reaction is seen in chronic allergic rhinitis, with hypersecretion and congestion as the most prominent symptoms. Priming can occur; it is characterized by a lowered threshold to stimulus after repeated allergen exposure. This repeated exposure causes a hypersensitivity reaction to one or many allergens. Sufferers may also become hyperreactive to nonspecific triggers such as cold air or strong odors. Rhinitis may be seasonal or perennial, allergic or nonallergic. Nonallergic rhinitis can be induced by infections, such as viruses, or associated with nasal polyps, as occurs in patients with aspirin idiosyncrasy. Medical conditions such as pregnancy or hypothyroidism can cause rhinitis, as can exposure to occupational factors or medications. The so-called NARES syndrome is a nonallergic type of rhinitis associated with eosinophils in the nasal secretions. It typically occurs in middle-aged individuals and is accompanied by some loss of sense of smell. Ideally, attempts-should-be-made-to-minimize-contact-with-the-suspected-allergen. If-dust-mite-sensitivity-issuspected, using allergen-proof covers for the mattress and pillows can improve symptoms. Washing sheets in hot water and removing carpets and drapes are other helpful strategies for reducing dust mite exposure. Saline alone can improve nasal stuffiness, sneezing, and congestion saline sprays usually cause no side effects and may be tried first in pregnant patients. Saline sprays are generally used to relieve mucosal irritation or dryness associated with various nasal conditions, minimize mucosal atrophy, and dislodge encrusted or thickened mucus. Also, if used immediately before intranasal corticosteroid dosing, saline sprays may help prevent drug-induced local irritative side effects. Antihistamines often serve as a foundation of symptomatic therapy. Terfenadine and astemizole, two nonsedating antihistamines, have been associated with a ventricular arrhythmia known as Torsades de Points, usually in interaction with other medications such as ketoconazole and erythromycin, or secondary to an underlying cardiac problem. To date loratadine, another nonsedating antihistamine, and cetirizine have not been associated with an adverse impact on the QT interval, or with adverse cardiovascular events. The most common side effect of cetirizine is drowsiness (14% vs. 6% on placebo). When used in recommended doses by patients without known risk factors, the non-sedating anti-histamines generally pose minimal risk for an adverse cardiac event. These drugs, e.g. Claritin, can be effective in relieving sneezing, runny nose, and nasal, ocular and palatal itching. Although not approved for this indication, some of the non-sedating agents may be useful in patients with asthma. Studies indicate that terfenadine, loratadine and astemizole exhibit modest bronchodilating effects, reduce bronchial hyperreactivity to histamine, and protect against exercise- and antigen-induced bronchospasm, although some of these benefits may require higher-than-currently-recommended doses. The sedating-type antihistamines may help people to sleep at night, but they cause sleepiness and compromise performance if taken during the day. Antihistamines are typically combined with a decongestant to help relieve nasal congestion.

Sympathomimetic medications are used as vasoconstrictors and decongestants. The three common systemic decongestants are pseudoephedrine, phenylpropanolamine and phenylephrine. These agents may cause hypertension, palpitations and tachycardia, as well as restlessness, insomnia and headache. The interaction of phenylpropanolamine with caffeine-in doses of two to three cups of coffee-may significantly raise blood pressure. In addition, medications such as pseudoephedrine can cause hyperactivity in children. Topical decongestants should be used only for a limited period of time, as they are associated with a rebound nasal dilatation with overuse. Anticholinergic agents have a role in patients with significant rhinorrhea or for specific entities such as "gustatory rhinitis," which is usually associated with ingestion of spicy foods. They also have been studied for their beneficial effects on the common cold. Cromolyn has a good safety record and is especially effective if used prophylactically. Administered via nasal spray, cromolyn can be effective in reducing sneezing, rhinorrhea, and nasal pruritus. It can block both early- and late-phase hypersensitivity responses. Although side effects are unusual, sometimes the spray will produce sneezing, transient headache, and even nasal burning. Topical corticosteroids such as Vancenase are very effective agents in the treatment of rhinitis, especially for symptoms of congestion, sneezing, and runny nose. Depending on the preparation, the corticosteroid nose sprays may cause irritation, stinging, burning, or sneezing. Local bleeding and septal perforation can also occur, especially if the aerosol is not aimed in the proper direction. Topical steroids generally are more effective than cromolyn sodium, and are particularly effective in the treatment of NARES. These agents can be highly effective in reducing the symptoms of rhinitis, but side effects limit their usefulness except for temporary therapy in patients with severe symptoms. These agents are particularly useful in shrinking nasal polyps when local therapy has been unsuccessful. Immunotherapy, while expensive and inconvenient, often can provide substantial benefits, especially for patients who experience side effects from other medications. The therapy is associated with production of so-called blocking antibodies, and with an alteration of cellular histamine release. Eventually, these changes result in decreased IgE, along with many other favorable physiologic changes. Because of the rising prevalence of IgE-mediated diseases, it is important to note the possible role of IgE-mediated hypersensitivity in atopic patients who suffer from recurrent middle ear infections. For allergic rhinitis sufferers, a runny nose is more than a nuisance. The disorder can impair quality of life and set the stage for more serious ailments including psychological problems. But it may be controlled. Presently available treatments may help to minimize symptoms, such as propranolol, verapamil, and adenosine. These have Food and Drug Administration-approved labeling for acute termination of supraventricular tachycardia (SVT).

Verapamil has been the most commonly used agent in the general population but it has several shortcomings, such as its potential to cause or exacerbate systemic hypotension, congestive heart failure, bradyarrhythmias, and ventricular fibrillation. In addition, verapamil readily crosses the placenta and has been shown to cause fetal bradycardia, heart block, depression of contractility, and hypotension. Adenosine has several advantages over verapamil, including rapid onset, brevity of side effects, theoretical safety, and probable lack of placental transfer. Adenosine ultimately may prove to be the preferred agent for termination of paroxysmal supraventricular tachycardia also in the gravid woman. Given the high numbers of deaths involving myocardial disease, the possibility of identifying individuals who are at risk is of great importance, because an early detection permits an early treatment of the

conditions. Electrocardiographic stress tests are used for this purpose while an individual exercises, but they lack high sensitivity and specificity. This is particularly the case with asymptomatic patients or with those with atypical toracic chest pain of angina. In this case, in addition to the excercise stress test, cardiac perfusion images are also obtained with γ rays, such as those emitted by 201 Th or 99 mTc. A good number of coronary patients, however, cannot excercise at a level acceptable to validate the results of the test, such as those afflicted with severe arthritis and peripheral vascular diseases or conditions, among others. Hypertensive patients taking β -blockers and calcium channel antagonists also present a problem as to the detection of an adequate pulse and an effective stress test result while exercising. It is for these groups of patients who may not exercise adequately that pharmacological stress tests are most useful. In the United States about a third of patients referred for myocardial perfusion tests are administered pharmacological tests. For these, as well as for patients attended to in general practice, two kinds of drugs are utilized: coronary vasodilating drugs and positive inotropic agents.

Only two coronary dilating agents have been approved by the FDA for use in this test: dipyrimidol and adenosine, both of which dilate coronary arteries by elevating the level of adenosine in blood and increasing 4 or 5-fold the coronary blood flow. Once these changes are imparted, the patient is administered intravenously a radioactive agent, such as ²⁰¹Ta or ⁹⁹mTc to do γ-ray imaging. Although in a normal person the distribution of the radiolabel would be uniform, in a subject with one or more stenosis or occlusions in the coronary arteries will exhibit areas or "defects" in the artery (ies) irrigated by the radioactive label of different intensity (ies), which is attributtable to ischemia or to myocardial necrosis. Contrary to those observed with exercise, the hemodynamic and electrocardiographic changes observed upon the administration of pharmacological agents like adenosine are slight. Usually the pulse will increase from 10% to 20% and the systemic arterial pressure from 5% to 10%, and the electrocardiographic depressions of the CT segments in the electrocardiogram (ECG) indicate a specific and serious sign of coronary artery disease. Thus, for many patients, the ability to undergo a pharmacological stress test is of extreme importance. However, many patients exhibit secondary effects (side effects), which in many cases result in severe bronchospasm, myocardial infarction and death. Thus, the administration of adenosine in a pharmacologic stress test is contraindicated in individuals afflicted with bronchoconstriction, asthma, including occult asthma, hypotension, and atrioventricular blockage of the second and third degrees. Many SVT patients and other subjects who would benefit from adenosine administration to assess their cardiovascular function, however, have hyper-responsive airways and are, thus, prone to bronchoconstriction in response to the administration of adenosine. This by itself, prevents them from being administered adenosine in order to avoid extreme bronchoconstriction, which may be life threatening.

The availability of a novel strategy to prevent and/or counter adenosine receptor-associated effects of disorders and conditions associated with symptoms such as pulmonary bronchoconstriction, impeded respiration, inflammation and allergy (ies), among others, of great practical importance. Such technology is clearly applicable to the treatment of heart, lung and kidney damage or failure, e.g. associated with hypoxia ailments including Acute Respiratory Disorder Syndrome (ARDS), asthma, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer,

lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer, would clearly find an immediate therapeutic application. Similarly, a composition and method which are suitable for administration before, during and after other treatments or diagnostic procedures, including radiation, chemotherapy, administration of radiocontrast agents, including those containing metal ions, antibody therapy, phototherapy and cancer, and other types of surgery, and adenosine such as in stress tests and in the treatment of SVT, among others, that may be effectively administered preventatively, prophylactically or therapeutically, and in conjunction with other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects is also of immediate clinical application.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition, which has cardiopulmonary and/or renal protective activity or which is effective for preventing or treating diseases and conditions such as ARDS, and those associated with ischemia or the release of endotoxins or with the administration of certain agents, including adenosine, e.g. for treating SVT, etc. Examples of these are septic and toxic shock and septicemia. The main component of the composition is a nucleic acid which comprises an oligonucleotide (oligo), which when administered to a subject is effective for alleviating or inhibiting the adenosine-mediated diseases and conditions described and many others. The oligos are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions such as intron and exon borders, e.g. the 5' end, the 3' end and the juxta-section between coding and non-coding regions, or to all segments of mRNA(s) encoding an adenosine A₁, A_{2a}, A_{2b} and A₃ receptors having A₁, A_{2b} and/or A_3 agonist activity or A_{2a} antagonist activity, (generally to any agent having adenosine A_{2a} agonist activity), anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions such as intron and exon borders selected from the group consisting of the 5' end, the 3' end or the juxta-section between coding and non-coding regions, or to analogues to these oligos consisting of less than about 15% adenosine (A), or mixtures thereof, and a physiologically acceptable carrier, and other agents such as diagnostic agents, e.g. radio-contrast media, other therapeutic agents for treating diseases or conditions or exogenous compounds which are associated with lung, heart or renal damage, e.g., glycerol, endotoxin and chemotherapeutic agents such as cisplatin and methotrexate, and formulation ingredients, among others. Examples of adenosine administration are in the treatment of SupraVentricular Tachycardia (SVT) and in stress tests in hyper-sensitized individuals. Side effects caused by the exogenous administration of adenosine, such as extreme respiratory difficulty, airway blockage, bronchoconstriction, allergy and inflammation, among others, are prevented and countered by the present agents and in some cases, depending on the dose administered, totally abolished. Other diseases or conditions afflict the kidneys and other organs and their functions by increasing levels of endotoxin, and the like. Many diseases and conditions are often associated with the development of ischemia or hypoxia which, by itself or through the release of other agent(s), is either associated with or brings about cardiopulmonary or renal damage and/or failure, and thus may benefit from the present invention as applied to protect the heart and kidneys. Thus, the pharmaceutical composition of the invention may be used to protect the lungs, heart and kidneys from damage associated or caused by other

diseases or conditions or the administration of therapeutic or diagnostic agents. In addition, the present composition may also be applied to the treatment of numerous conditions which, in its absence, might produce considerable heart, lung and kidney damage and even failure, by addition of one or more therapeutic agents for treating the disease or condition as well as the agent described in this patent. For example, a pharmaceutical composition in accordance with the invention might comprise an anti-cancer agent and the lung, heart and kidney protecting agent of the invention, in amounts effective for treating cancer and for preventing kidney damage, respectively. In another example, the present agent in combination with other therapeutic agents, including anti-cholinergic agents, and the like, may be used to treat food poisoning when endotoxins are released by microorganisms such as the Botulinium family and others, or to treat snake poisoning such as when endotoxin is released, etc., while protecting the subject from the effects of endotoxins, including septic shock and septicemia. Similarly, the present composition may be utilized to protect a subject from renal damage while conducting a diagnostic procedure containing an agent which has deleterious pulmonary, cardiac and/or renal effects, by separately administering or combining in one composition the agent of the invention and a diagnostic agent. The present composition is also suitable for treating harm associated with the administration of substances like adenosine, cysplatin, radiocontrast agents and glycerol, routinely used for diagnostic and therapeutic purposes.

The agents of this invention may be formulated for administration by various different routes, such as topical and systemic, e.g. oral, parenteral, inhalable, and the like, and are generally administered in amounts which prevent or reduce adenosine-mediated side effects such as bronchoconstriction, allergy(ies), inflammation and airway obstruction, among others. The present compositions and formulations, thus, are suitable for the prevention and alleviation of adenosine-mediated bronchoconstriction, allergy and/or inflammation, which are associated with the administration of adenosine in the treatment of SVT and in stress tests to hyper-sensitized individuals. These agents may be administered by themselves or in conjunction with adenosine or similar acting drugs, and in a preventative as well as therapeutic course.

The present composition and formulations may thus be applied to the prevention or alleviation of adenosine receptor-mediated cardiopulmonary and/or renal damage or failure, such as occurs in subjects afflicted with ischemia and as a consequence of the administration or release in the organism of certain compounds such as glycerol, endotoxin, cisplatin, or radiocontrast agents used for imaging purposes, or other agents which are administered for therapeutic or diagnostic purposes, or as a consequence of an accident. The formulations of this invention, e.g. topical, oral, parenteral, inhalable, and the like, also reduce adenosine-mediated bronchoconstriction and/or help to prevent or treat ARDS symptoms. The formulations may be administered to a subject by themselves or in conjunction with other therapies that are known in the art. The present composition is effective to alleviate bronchoconstriction, lung allergy(ies) and inflammation, cardiopulmonary and renal diseases and conditions, e.g. renal damage and faulure, hypoxia, ARDS, COPD, etc., as well as cardiopulmonary effects (deleterious) associated with the administration of certain diagnostic and therapeutic agents, and optionally comprising a surfactant, and the oligo described here. Generally, the oligos are anti-sense to an adenosine A_1 , A_{2a} , A_{2b} or A_3 receptor and exhibit adenosine A_1 , A_{2b} or A_3 receptor inhibitory activity or adenosine A_{2a} agonistic activity, and analogues thereof wherein A_{1} is substituted by a universal base that binds to thymidine.

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Moreover, any adenosine A2 agonist is encompassed by this invention, not only anti-sense oligos. These analogues evidence either reduced adenosine content or reduced adenosine receptor activating activity. The above composition is generally administered in an amount which prevents or reduces adenosine receptor associated side effects such as bronchoconstriction, allergy(ies), inflammation and airway obstruction, lung, heart and kidney damage, among others. The present compositions and formulations. thus, are suitable for the prevention and alleviation of adenosine receptor associated bronchoconstriction, allergy and/or inflammation and, therefore, in the treatment of Acute Respiratory Disorder Syndrome (ARDS), asthma, side effects associated with adenosine administration in SupraVentricular Tachycardia (SVT) and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer, among others. These compositions are also suitable for use in the prevention and treatment of adenosine-receptor mediated effects brought about by the administration of exogenous agents. The present technology is also applicable in conjunction with other procedures and/other therapies, including other therapeutic agents such as antibody therapy and chemotherapy, among others, radiation, phototherapy, and cancer and other types of surgery, and is effectively administered preventatively, prophylactically or therapeutically. The present pharmaceutical formulations may be administered to a subject in need of such treatment in amounts comprising an anti-renal damage or failure effective amount of the oligo of the invention, and optionally other agents having specific activities, carriers and other formulation ingredients as known in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the effects of A₁ adenosine receptor anti-sense oligonucleotides and mismatch control anti-sense oligonucleotides on the dynamic compliance of the bronchial airway in a rabbit model. The two stars represent significant difference at p<0.01, Student's t-test.

Figure 2 illustrates the specificity of A_1 adenosine receptor anti-sense oligonucleotides as indicated by the A_1 and A_2 adenosine receptor number present in airway tissue treated with A_1 adenosine receptor anti-sense oligonucleotides.

Figures 3a and 3b illustrate the response of two hyper-responsive monkeys (ascaris sensitive) to a challenge with inhaled adenosine. The right hand bar represents the PC₄₀ adenosine after administration of the Oligo I, whereas the left hand bar represents the PC₄₀ adenosine value prior to treatment with the Oligo I. The PC₄₀ adenosine, represented in the Y axis, is the amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways.

Figure 3a represents the experimental results obtained without and with pre-treatment of a first monkeys with a phosphorothicate agent of the invention (anti-sense oligo I; SEQ. ID NO: 1), prior to administration of adenosine.

Figure 3b represents the experimental results obtained without and with pre-treatment of a

second monkey with a phosphorothioate agent of this invention (anti-sense oligo I; SEQ. ID NO:1), prior to administration of adenosine.

Figure 4 shows the effect on surfactant in an experimental animal. Figure 4a shows the baseline level of surfactant in the rabbit. Figure 4b shows the level of surfactant after administration of adenosine (Post adenosine challenge). Figure 4c shows the level of surfactant upon administration of an adenosine A₁ anti-sense oligonucleotide (SEQ. ID NO: 1) and then adenosine.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One aspect of this invention arose from a desire by the inventor to improve on his own prior technology for the treatment of acute bronchoconstriction, allergy and/or inflammation associated with various diseases and conditions and as an improvement on ineffective existing methods for treating diseases and conditions such as Acute Respiratory Distress Syndrome (ARDS), allergic rhinitis, asthma, adenosine administration e.g. in the treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to adenosine hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. Extremely dangerous, and in many cases lethal, effects are encountered when adenosine receptors are activated by adenosine, administration. The activation of the adenosine A₁ receptor, in particular, may cause life threatening, and in some cases even fatal, bronchoconstriction in hyper-responsive individuals. The inventor, in addition, wanted to provide a treatment which would improve the outcome and life style of patients undergoing other procedures or being administered other therapies, including antibody therapy, chemotherapy, radiation, phototherapy, and surgery e.g. cancer surgery, and that could be effectively administered preventatively, prophylactically or therapeutically.

He succeeded in this endeavor and is providing in this patent novel and improved compositions, formulations and methods which afford greatly improved results when compared with previously known treatments for preventing and alleviating bronchoconstriction, allergy(ies), inflammation, breathing difficulties and blockage of airways, cardiopulmonary and renal damage, and the like. The nucleic acid, and optional surfactant and other components, of the composition of the invention may be formulated alone with a carrier, or with other therapeutic agents and formulation agents as is known in the art. The compositions of this invention, thus, may be incorporated into a variety of formulations for systemic and topical administration.

The present composition and treatment are applicable to avoiding cardiopulmonary and renal damage, such as that seen in association with ischemic or hypoxic conditions as well as with the administration of radio-contrast media, and certain other agents, e.g. those known to cause ischemia and/or to produce cardiopulmonary and/or renal damage or failure, such as such as radiocontrast agents, glycerol and chemotherapeutic agents such as methotrexate and cisplatin. In addition, the inventor found that the present technology is suitable for the prevention and treatment of renal damage and failure such

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as is produced in food and snake poisoning as well as septicemia and septic or toxic shock caused by the release of endotoxins, such as when microorganisms of the type Botulinum, and the like, are ingested, or even from unknown sources.

To his surprise, the inventor found that the present agent had a protective effect with respect to the heart, lung and kidneys, and that it could be administered prophylactically as well as therapeutically. In addition, when specific other agents are included the present composition may also be applied to the treatment of diseases and conditions where the other agents have a secondary deleterious cardiopulmonary or renal effect, including diseases and conditions associated with ischemia, the administration of adenosine, e.g. for the treatment of SVT or in stress tests, for the treatment of cancer, e.g. by administration of an anti-cancer drug such as cisplatin and the oligo of this invention. Thus, the anti-sense oligonucleotide (oligo) of the invention may be administered as a variety of formulations, either by itself, with or without a surfactant, or with other agents. The anti-sense oligonucleotide of this invention, thus, may be incorporated into a variety of formulations for systemic and topical administration.

The present invention also improves on the state of the art for rescuing patients afflicted with ARDS, whether as a consequence of multiple traumatic injury, severe blood infections such as sepsis, or other systemic illness, the administration of high dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure, and in many cases death. Although a large number of persons are afflicted with this disease or condition every year, up to the present time, no measures to prevent ARDS have been available. ARDS has been and still is considered to be untreatable, and the only palliative treatment has been limited to compensating for the severe dysfunction of the respiratory system and treating the underlying cause of the lung injury. One of the fastest developing symptoms in ARDS is hypoxia, which is generally treated by administration of hyperbaric oxygen, often at high concentrations. The inventor extensively investigated the etiology of Respiratory Distress Syndrome (RDS) and ARDS and other conditions which appear to trigger ARDS, and is hereby proposing the implementation of a prophylactic or preventative and therapeutic treatment based on the administration of oligonucleotides, with or without vectors linked to them designed to treat the acute impairment of the airways, bronchoconstriction, allergy and/or inflammation symptoms seen in patients who develop ARDS. The present composition, formulations and methods are, thus, applicable to the prophylaxis of ARDS immediately after a potential diagnosis is made that a patient is a good candidate for developing the condition. In addition, and given that ARDS symptoms many times develop extremely fast, the present technology is also applicable to the treatment of patients who are already afflicted with the respiratory and inflammatory symptoms seen in ARDS. The present composition and formulations may be administered by themselves or in conjunction with other ancillary agents directed to alleviating ARDS symptoms, such as oxygen-enriched air, surfactants, blood pressure controlling agents, and the like. The composition of the invention is provided in a variety of formulations for systemic and topical administration, which may utilized as prescribed by a clinician.

The present inventor unexpectedly found that the agents of the invention, particularly those which have at least some inhibitory activity over the adenosine A₁ receptor, strongly inhibit, and in some cases terminate, with 100% efficacy, the acute respiratory and inflammatory symptoms of ARDS. Experimental work, some of which is provided in the examples of this patent, has shown a complete

interference with, and cessation of, bronchoconstriction and other unwanted side effects associated with ARDS, which are mediated by adenosine receptor(s) in each of two animal models of human bronchial hyper-responsiveness: a hyper-responsive rabbit model and a hyper-responsive cynamologous monkey model, both being widely acknowledged by the scientific community as models for bronchoconstriction, allergy and inflammation involving the respiratory airways in humans. The agents of this invention, therefore, have been shown to prevent and counter these ARDS-associated symptoms, associated with adenosine receptors, possibly with an adenosine A₁ receptor. The prevention and suppression of ARDS symptomatology seen upon administration of the agent of this invention is clearly applicable to the prevention of ARDS and to the treatment of patients afflicted by this condition by itself, either prior to, simultaneously with, and subsequent to other palliative therapy. The present invention now is set to save a large number of previously unnecessarily lost lives, given the high morbidity and mortality associated with ARDS.

Respiratory distress syndrome (RDS) occurs in preterm infants ("preemies"), and is an extremely serious problem. A primary cause of RDS in such preterm infants is the immature developmental stage of the infant, resulting in low levels or lack of surfactant, a material critical for normal respiration. Preterm infants or "premies" exhibiting RDS are ventiliated, and administered oxygen and surfactant preparations. When they survive, infants with RDS frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease (CLD) of early infancy. This condition too is often fatal.

The causes of surfactant depletion in the preterm infant are unknown. However, it is known that surfactant secretion is upregulated through adenosine A2a receptors and inhibited through adenosine adenosine A₁ receptors. It has been shown that ATP and A₁ adenosine receptor agonists mobilize intracellular calcium and activate potassium and chloride currents in normal and cystic fibrosis airway epithelial cells. Furthermore, the adenosine A1 receptor is also known to participate in the protection of tissues from the effects of oxygen deprivation or hypoxia. Based on these and other pieces of information, the inventor hypothesized that, during normal fetal development, there is a changing (increasing) ratio of the adenosine A_{2a} receptor to the adenosine A₁ receptor (A_{2a}:A₁ ratio), such that the A₁ receptor protects fetal lung tissues during fetal anoxia and inhibits premature surfactant secretion. The adenosine A1 receptor expression decreases as the fetus approaches term. Conversely, he hypothesized that the adenosine A2a receptor is less expressed in early fetal stages, and its expression increases as the fetus approaches term, ensuring normal levels of surfactant secretion upon birth. In the pre-term infant, an existing high adenosine A₁:A_{2a} ratio does not have an opportunity to reverse itself because the infant is born before adequate adenosine A2a receptor expression occurs and while there is still significant adenosine A₁ expression. This causes decreased surfactant production at birth and thereafter. Accordingly, he surmised that the administration of an adenosine A₁ anti-sense oligonucleotide would reduce the level of adenosine A₁ receptor formed. In addition, he also surmised that the administration of any adenosine A2a agonist, whether or not an oligonucleotide, would specifically stimulate this receptor. Either therapy or a combination of both would be suitable for treating RDS, particularly in "preemies."

Rhinitis is not a disease, it is a term describing a group of symptoms produced by nasal irritation

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or inflammation. Allergies, however, including allergic rhinitis, affect an estimated 40 to 50 million people in the United States. Some allergies may interfere with day-to-day activities or lessen the quality of life. Rhinitis is a term describing the symptoms produced by nasal irritation or inflammation. Symptoms of rhinitis include runny nose, itching, sneezing and stuffy nose due to blockage or congestion. These symptoms are the nose's natural response to inflammation and irritation. Arbitrarily, rhinitis lasting less than six weeks is called acute rhinitis, and persistent symptoms are called chronic rhinitis. Acute rhinitis is generally caused by infections or chemical irritation. Chronic rhinitis may be caused by allergy or a variety of other factors. The nose normally produces mucus, which traps substances like dust, pollen, pollution, and germs such as bacteria and viruses. Mucus flows from the front of the nose and drains down the back of the throat. When mucus production is excessive, it can flow from the front, as a runny nose, or become noticeable from the back, as post-nasal drip. Nasal mucus, normally a thin, clear liquid, can become thick or colored, perhaps due to dryness, infection or pollution. When post-nasal drip is excessive, thick, or contains irritating substances, cough is the natural response for clearing the throat. Itching and sneezing are also natural responses to irritation caused by allergic reactions, chemical exposures including cigarette smoke, or temperature changes, infections and other factors. The nasal tissues congest and decongest periodically. In most people, nasal congestion switches back and forth from side to side of the nose in a cycle several hours long. Some people, especially those with narrow nasal passages, notice this nasal cycle more than others. Strenuous exercise or changes in head position can affect nasal congestion. Severe congestion can result in facial pressure and pain, as well as dark circles under the eyes. Sinusitis is inflammation or infection of any of the four groups of sinus cavities in the skull, which open into the nasal passages. Sinusitis is not the same as rhinitis, although the two may be associated and their symptoms may be similar. The terms sinus trouble or sinus congestion are sometimes wrongly used to mean congestion of the nasal passage itself. Most cases of nasal congestion, though, are not associated with sinusitis. Known to most people as hay fever, allergic rhinitis is a very common medical problem affecting more than 15 percent of the population, both adults and children. Allergic rhinitis takes two different forms seasonal and perennial. Symptoms of seasonal allergic rhinitis occur in spring, summer and/or early fall and are usually caused by allergic sensitivity to pollens from trees, grasses or weeds, or to airborne mold spores. Other people experience symptoms year-round, a condition called perennial allergic rhinitis. It is generally caused by sensitivity to house dust, house dust mites, animal dander and/or mold spores. Underlying or hidden food allergies are considered a possible cause of perennial nasal symptoms. Some people may experience both types of rhinitis, with perennial symptoms worsening during specific pollen seasons. There are, however, other causes for rhinitis. When a sensitive person inhales an allergen (allergy-causing substance) like ragweed pollen, the body's immune system reacts abnormally with the allergen. The allergen binds to allergic antibodies (immunoglobulin E) that are attached to cells that produce histamine and other chemicals. The pollen " triggers " these cells in the nasal membranes, causing them to release histamine and the other chemicals. Histamine dilates the small blood vessels of the nose and fluids leak out into the surrounding tissues, causing runny noses, watery eyes, itching, swelling and other allergy symptoms. Antibodies circulate in the blood stream, but localize in the tissues of the nose and in the skin. This makes it possible to show the presence of these antibodies by skin testing, or less commonly, by a special blood test. A positive skin test mirrors the type of reaction going on in the nose. Hay fever is a turn-of-

the-century term which has come to describe the symptoms of allergic rhinitis, especially when it occurs in the late summer. However, the symptoms are not caused by hay (ragweed is one of the main culprits) and are not accompanied by fever. So physicians prefer the term " allergic rhinitis" because it is more accurate. Similarly, springtime symptoms are sometimes called rose fever but it's just coincidental that roses are in full-bloom during the grass-pollinating season. Roses and other sweet-smelling, showy flowers rely on bees, not the wind, for pollination, so not much of their pollen gets into the air to cause allergies.

A common question from allergic rhinitis sufferers is whether they may relocate to a place where their allergies will go away. Some allergens are tough to escape. Ragweed which affects 75% of allergic rhinitis sufferers blankets most of the United States. Less ragweed is found in a band along the West Coast, the southern-most tip of Florida and northern Maine, but it is still present. Even Alaska and Hawaii have a little ragweed . A move may be of questionable value because a person may escape one allergy to ragweed, for example only to develop sensitivity to grasses or other allergens in the new location. Some known complications include ear infections, sinusitis, recurrent sore throats, cough, headache, fatigue, irritability, altered sleep patterns and poor school performance. Occasionally, children may develop altered facial growth and orthodontic problems. In some cases, allergy treatment can eliminate or alleviate most of these problems. Rhinitis may result from many causes other than allergic reaction. Not all rhinitis symptoms are the result of allergies. The following are the three most common causes of rhinitis with some of their characteristics: Rhinitis or Allergic Sensitivity is generally caused by allergic hay fever dust, foods, animals, pollens, molds, perennial and/or seasonal infectious colds or flu viruses, bacteria, and others, and generally lasts 3-7 days. Non-allergic rhinitis may be caused by irritant smoke, air pollution, exhaust fumes, aerosol sprays, fragrance, paint fumes, etc. The most common condition causing rhinitis is the common cold, an example of infectious rhinitis. Most infections are relatively short-lived, lasting from three to seven days. Colds can be caused by any one of more than 200 viruses. Children, particularly young children in school or day care centers, may have from eight to 12 colds each year. Fortunately, the frequency of colds lessens after immunity has been produced from exposure to many viruses. Colds usually begin with a sensation of congestion, rapidly followed by runny nose and sneezing. Over the next few days, congestion becomes more prominent, the nasal mucus may become colored, and there may be a slight fever and cough. Cold symptoms resolve within a couple of weeks, although a cough may sometimes persist. Cold symptoms that last longer may be due to other causes, such as chronic rhinitis or sinusitis. Allergic rhinitis very often has no cure. Most treatments aim at keeping its symptoms under control by avoiding or reducing exposure to substances that cause symptoms and by taking medication when needed.

Dryness of the nasal tissues can be a normal effect of aging, or a characteristic of a nasal condition associated with a foul smelling nasal discharge. Rhinitis can also be a feature of endocrine disease, like hypothyroidism, or can occur during pregnancy. Rhinitis can be made worse or even improved during pregnancy. Alcoholic beverages can cause the blood vessels in the nose to enlarge temporarily and produce significant nasal congestion. Sometimes several conditions can coexist in the same person. In a single individual, allergic rhinitis could be complicated by vasomotor rhinitis, septal deviation (curvature of the bone separating the two sides of the nose) or nasal polyps. Use of spray decongestants for chronic sinusitis, septal deviation or vasomotor rhinitis may cause rhinitis

medicamentosa. Any of these conditions will be made worse by catching a cold. Nasal symptoms caused by more than one problem can be difficult to treat, often requiring the cooperation of an allergistimmunologist and an otolaryngologist (ear, nose and throat specialist). Once allergic rhinitis is diagnosed, treatment options include avoidance, medication and immunotherapy (allergy shots), neither of which offers a complete cure. A single ragweed plant may release one million pollen grains in just one day. The pollen from ragweed, grasses and trees is so small and buoyant that the wind may carry it miles from its source. Mold spores, which grow outdoors in fields and on dead leaves, also are everywhere and may outnumber pollen grains in the air even when the pollen season is at its worst. While it's difficult to escape pollen and molds, exposure may be lessened by keeping windows closed, using air-conditioning in the summer and a HEPA (High Energy Particulate Air) filter or an electrostatic precipitator to clean pollen and mold from the air. Early morning is a good time to limit outdoor activities because outdoor air is most heavily saturated with pollen and mold between 5 and 10 a.m., etc. Other than avoidance measures, medications such as antihistamines and decongestants are the most commonly used for allergic rhinitis. Newer medications, such as cromolyn, inhibit the release of chemicals that cause allergic reactions. Nasal corticosteroid sprays reduce the inflammation from the allergic trigger. Medications help to alleviate nasal congestion, runny nose, sneezing and itching. They are available in many forms, including tablets, nasal sprays, eye drops and liquids. Most of these medications cause side effects. Allergen immunotherapy, known as allergy shots may be recommended for persons who don't respond well to treatment with medications, experience side-effects from medications or have allergen exposure which is unavoidable. Immunotherapy, however, does not cure allergies but can be very effective in controlling allergic symptoms. Allergy injections are usually given at variable intervals over a period of three to five years. An immunotherapy treatment program may consist of injections of a diluted allergy extract, administered frequently in increasing doses until a maintenance dose is reached. Then, the injection schedule is changed so that the same dose is given with longer intervals between injections. Immunotherapy helps the body build resistance to the effects of the allergen, reduces the intensity of symptoms caused by allergen exposure, and sometimes can actually make skin test reactions disappear. As resistance develops, symptoms should improve, but the improvement from immunotherapy will take several months to occur. Immunotherapy does not help the symptoms produced by non-allergic rhinitis.

Antihistamines are the most inexpensive and commonly used treatment for rhinitis. These medications counter the effects of histamine, the irritating chemical released within your body when an allergic reaction takes place. Although other chemicals are involved, histamine is primarily responsible for causing the symptoms. Antihistamines do not cure, but help relieve: nasal allergy symptoms, such as sneezing, itching and discharge; eye symptoms, such as itching, burning, tearing, and clear discharge; skin conditions, such as hives, eczema, itching and some rashes; and other allergic conditions as determined by your physician. There are dozens of different antihistamines and wide variations in how patients respond to them. Some are available over-the-counter and others require a prescription. Generally, they work well but produce side effects. The body tends to build up resistance to some antihistamines over time. This tendency varies from individual to individual. Persons with nasal dryness or thick nasal mucus should avoid taking antihistamines without consulting a physician. Contact your physician for advice if an antihistamine causes drowsiness or other side effects. Short-acting

antihistamines can be taken every four to six hours, while timed-release antihistamines are taken every 24 hours. The short-acting antihistamines are often most helpful taken 30 minutes before anticipated allergic exposure (picnic during ragweed season). Timed-release antihistamines are better suited to chronic (long-term) use for those who need daily medications. The most common side effect is sedation or drowsiness. For this reason, it is important that you do not drive a car or work with dangerous machinery the first time you take an antihistamine. You should take the antihistamine for the first time at home, several hours before bedtime. When you are sure that the medicine will not cause sedation, you then can take it any time as prescribed during the day. In persons who experience drowsiness, the sedation effect usually lessens over time. Some of the newer antihistamines produce low drowsiness. Another frequently encountered side effect is excessive dryness of the mouth, nose, and eyes. Less common side effects include restlessness, nervousness, over excitability, insomnia, dizziness, headaches, euphoria, fainting, visual disturbances, decreased appetite, nausea, vomiting, abdominal distress, constipation, diarrhea, increased or decreased urination, high or low blood pressure, nightmares (especially in children), sore throat, unusual bleeding or bruising, chest tightness or palpitations. Alcohol and tranquilizers increase the sedation side effects of antihistamines and, therefore, must be avoided during therapy.

Decongestants help relieve the stuffiness and pressure caused by allergic, swollen nasal tissue. They do not contain antihistamines, so do not cause antihistamine side effects. They do not relieve the other symptoms of allergic rhinitis, such as runny nose, post-nasal drip and sneezing. Decongestants are available as prescription and non-prescription medications and are often seen in combination with antihistamines or other medications. It is not uncommon for patients using decongestants to experience insomnia if taking the medication in the afternoon or evening. If this occurs, a dose reduction may be needed. At times, men with prostate enlargement may encounter urinary problems while on decongestants. Patients using medications for the management of emotional or behavioral problems should discuss this with their physicians before using decongestants. Pregnant patients should also check with their physician before starting decongestants. Non-prescription decongestant nasal sprays work within minutes and last for hours, but may not be used for more than a few days at a time without a physician's order. Oral decongestants are found in many over-the-counter and prescription medications, and may be the treatment of choice for nasal congestion. They don't cause rhinitis medicamentosa, but need to be avoided by some patients with high blood pressure. If you have high blood pressure, you should check with your physician before using them. Non-prescription saline nasal sprays help counteract symptoms of dry nasal passages or thick nasal mucus. Unlike decongestant nose sprays, a saline nose spray can be used as often as needed. Sometimes, your physician may recommend washing (douching) of the nasal passage. Corticosteroids counteract the inflammation caused by the body's release of allergy-causing substances, as well as that caused by other non-allergic factors. Thus, they generally work for many causes of rhinitis symptoms and are sometimes useful for chronic sinusitis. Corticosteroids are sometimes injected or taken orally, but usually on a short-term basis for extremely severe symptoms. Physicians warn that injected or oral steroids may produce severe side effects when used for long periods or used repeatedly and, for this reason, they should be used with extreme caution. In rhinitis, a corticosteroid is much safer when used by spraying it into the nose. Side effects are less common, but may include nasal ulceration, nasal fungal infection, or bleeding. Cromolyn is a medication

that blocks the body's release of allergy-causing substances. It does not work in all patients. The full dosage is four times daily, and improvement may take several weeks to occur. Atropine and the related drug ipratropium bromide are sometimes used to relieve the runny nose of rhinitis; in fact, most antihistamines have a slight atropine-like effect. Atropine can be taken orally and as a nasal spray. It is a component of some antihistamine decongestant preparations. Antibiotics are for the treatment of bacterial infections. They do not affect the course of uncomplicated common colds, and are of no benefit for non-infectious rhinitis, including allergic rhinitis. In chronic sinusitis, antibiotics may help only temporarily, and surgery may be needed. Eye allergy preparations are used when the eyes are affected by the same allergens that trigger rhinitis, causing redness, watery eyes and itching. Eye preparations are available as prescription and non-prescription medications.

All of the non-prescription antihistamines (combined with decongestants) are " first generation" antihistamines and generally cause drowsiness, slowed reaction time and dry mouth in most people. Examples are Actifed (and combination products), Alka Seltzer Plus Sinus Allergy Medicine, Allerest (and combination products), A.R.M., BC Cold Powder Multi-Symptom Formula, Benadryl (and combination products), Chlor-Trimeton (and combination products), Comtrex Multi-Symptom Day/Night, Contac Maximum Strength, Coricidin (and combination products), Dimetane, Dimetapp (and combination products), Drixoral (and combination products), PediaCare Night Rest Cough-Cold Liquid, Sinarest, Sudafed Plus, Tavist (and combination products), Triaminic Allergy, Tylenol Allergy Sinus/Tylenol PM, Vicks NyQuil (and combination products) and Vicks Pediatric Formula 44M Cough & Cold, among others. The following medications are second generation antihistamines and generally do not cause the extreme degree of side effects of first generation antihistamines, such as drowsiness, slowed reaction time and dry mouth. Examples of prescription antihistamines are Allegra, Claritin, Hismanal and Zyrtec. The latter may cause cardiac problems when combined with certain other medications whereas Hismanol has low sedating side effects. The following contain first generation antihistamines and generally cause drowsiness, slowed reaction time and dry mouth: Atarax, Antivert, Dallergy, Naldecon, Periactin, Rynatan, Temaril, Trinalin and Vistaril. The following are examples of non-prescription oral decongestants: Actifed Allergy Daytime, Allerest, Drixoral Non-Drowsy Formula, Efidac/24, PediaCare Infants' Decongestant Drops and Sudafed Tablets. Examples of prescription oral decongestants are DuraVent, Entex LA, Entex PSE, Exgest LA, Respaire, Sinuvent and Guaifed PD. Examples of non-prescription decongestant nasal sprays are Afrin and related products, Cheracol, Dristan, Duration 12-Hour, 4-Way Fast Acting and NTZ Long Acting. Their prolonged use, however, may cause rebound congestion. Other examples are Neo Synephrine and related products, Nostril/Nostrilla, Otrivin, Privine and Vicks Sinex Long-Acting/Vapor/Vaporub/VapoSteam/Vatronol. An example of non-prescription anti-allergy nasal spray is Nasalcrom, and of non-prescription saline nasal sprays are Afrin Saline Mist, Ayr, NaSal Moisturizer AF, Ocean and Salinex. An example of a prescription antihistamine nasal spray is Astelin. Examples of prescription atropine-like nasal sprays are Atrovent and Prescription nasal corticosteroid sprays, which do not contain antihistamines or decongestants. Other therapeutic agents suitable for the treatment of allergic rhinitis are Beconase (Pockethaler and Beconase AQ), Flonase, Nasacort (Nasal Inhaler and Nasacort AQ), Nasalide, Rhinocort and Vancenase (Pockethaler and Vancenase DS). Examples of prescription oral corticosteroids that do not contain antihistamines are Deltasone, Liquid Pred, Medrol,

Pediapred and Prelone.

The present inventor surmised that the administration of the present gents would be effective for the treatment of allergic rhinitis whose symptoms are mediated by adenosine receptors. In addition, the inventor showed the effectiveness of the present therapy, for example, on the level of surfactant in the lung in an animal model in which the adenosine A_1 receptor is known to be highly expressed, the allergic rabbit lung. See, Ail, S. et al., Adenosine-induced bronchoconstriction in allergic rabbit model, Am. J. Physiol. 266:L271-277 (1994); Ali, S. et al., Adenosine-induced bronchoconstriction and contraction of airway smooth muscle from allergic rabbits with late-phase airway obstruction: Evidence for an inducible adenosine adenosine A_1 receptor, JPET 268(3):1328-1334 (1994). In the normal lung, the adenosine A_1 receptor is generally not expressed, whereas the adenosine A_{2a} receptor is expressed. The experimental set-up and results are shown in Example 37 below.

In the past, anti-sense oligonucleotides received considerable theoretical consideration as being potentially useful as pharmacologic agents for the treatment of human disease. R. Wagner, Nature 372: 333-335 (1994). However, it has been difficult to actually apply them to alleviating and curing human diseases. One important consideration in the pharmacologic application of these molecules has been the failure of various routes of administration to deliver the compounds to its target while avoiding invading the circulation and, therefore, other untargeted tissues which, thus, produces a plethora of side effects. Most in vivo experiments utilizing anti-sense oligonucleotides involved a direct application of the oligo to limited regions of the brain. See, C. Wahlestedt, Trends in Pharmacol. Sci. 15: 42-46 (1994); J. Lai et al., Neuroreport 5: 1049-1052 (1994); K. Standifer et al., Neuron 12: 805-810 (1994); A. Akabayashi et al., Brain Res. 21: 55-61 (1994). Others applied them into the spinal fluid. See, e.g. L. Tseng et al., European J. Pharmacol. 258: R1-3 (1994); R. Raffa et al., European J. Pharmacol. 258: R5-7 (1994); F. Gillardon et al., European J. Neurosci. 6: 880-884 (1994). Such applications, clearly, have no clinical utility due to their invasive nature. Thus, the systemic administration of anti-sense oligonucleotides poses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues.

The systemic administration of anti-sense oligonucleotides also possesses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues. The respiratory system, and in particular the lung, as the ultimate port of entry into the organism, however, is an excellent route of administration for anti-sense oligonucleotides. This is so not only for the treatment of lung disease, but also when utilizing the lung as a means for delivery, particularly because of its non-invasive and tissue-specific nature. Thus, local delivery of antisense oligonucleotides directly to the target tissue enables the therapeutic use of these compounds. Fomivirsen (ISIS 2302) is an example of a local drug delivery into the eye to treat cytomegalovirus (CMV) retinitis, for which a new drug application has been filed by ISIS. The administration of a drug through the lung offers the further advantage that inhalation is non-invasive whereas direct injection in to the vitreous of the eye is invasive.

The composition and formulations of this invention have been shown to have an exceedingly high efficacy for preventing and treating a disease or condition associated with bronchoconstriction, difficult breathing, impeded and obstructed lung airways, allergy(ies) and/or inflammation. The examples provided below show a complete inhibition of such adenosine receptor associated symptoms in

a rabbit model for human bronchoconstriction, allergy(ies) and inflammation as well as the elimination of the ability of the adenosine receptor agonist par excellence, adenosine, to cause bronchoconstriction in hyper-responsive monkeys, which are animal models for human hyper-responsiveness to adenosine receptor agonists. The pharmaceutical composition and formulations of the invention, therefore, are suitable for preventing and alleviating the symptoms associated with stimulation of adenosine receptors, such as the adenosine A1 receptors. The compositions and formulations of this invention, thus, are also suitable for prevent the untoward side effects of adenosine-mediated hyperresponsiveness in certain individuals, which are generally seen in diseases affecting respiratory activity. Examples of diseases and conditions, which may be treated preventatively, prophylactically and therapeutically with the compositions and formulations of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, Acute Respiratory Distress Syndrome (ARDS), lung, heart and renal damage and failure, e.g. associated with ischemia as well as the administration of certain drugs, side effects associated with adenosine administration, e.g. in SupraVentricular Tachycardia (SVT) and in adenosine stress tests, infantile Respiratory Distress Syndrome (infantile RDS), pain, cystic fibrosis (CF), pulmonary hypertension, allergic rhinitis pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all other metastatic cancers, e.g. cancers which metastasized to the lung(s), breast and prostate. The present compositions and formulations are suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. The present compositions and formulations may also be administered effectively as a substitute for therapies that have significant negative side effects.

All nucleotide sequences are represented in this patent by a single strand only, and in the 5' to 3' direction, from left to right. All nucleotide and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR § 1.822 and established usage. See, e.g., PatentIn User Manual, 99-102 (Nov. 1990) (U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, D.C. 20231); U.S. Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43. The relevant sections of the disclosures of the above cited, and of all other patents and references cited in this patent are incorporated herein by reference.

The method of the present invention may be used as well to reduce adenosine-mediated heart, lung and kidney damage or failure resulting from any reason, including, but not limited to, ischemia, septicemia, septices shock, and the like, the administration of certain compounds such as radiocontrast agents used for imaging and diagnostic purposes, many of which have metal atoms, adenosine used for treating SVT and in stress tests, and the like. The method of the present invention may be used as well to reduce adenosine receptor associated bronchoconstriction in the lungs of a subject for any reason, including, but not limited to, bronchoconstriction, allergy(ies) and/or inflammation, such as those associated with COPD, ARDS, allergic rhinitis, pulmonary vasoconstriction, asthma, the administration of certain exogenous agents, pain, CF, emphysema, and cancer, among others. The compositions and formulations of the invention comprise a surfactant and an oligonucleotide which is anti-sense to the

adenosine A_1 , A_{2b} and A_3 receptors have shown to be effective in the down-regulation of the adenosine A_1 , A_{2a} , A_{2b} or A_3 receptors, respectively, in the cell. Others which are anti-sense to the adenosine A_{2a} receptor are also effective as long as they have some adenosine A_1 inhibitory activity or adenosine A_{2a} agonist activity. Similarly, non nucleic acid A_{2a} agonists are suitable. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction and other symptoms, is that the compositions and formulations of this invention may be administered directly into the respiratory system of an individual, and even to his\her lungs. In addition, the present treatment may reduce the amount or level of a receptor protein itself rather than merely acting at the receptor as is the case with treatments and/or where the agent is merely an antagonist acting at the receptor site. The selective characteristic of the present compositions and formulations along with their administration by a selected route results in reduced toxicity.

The present composition, formulations and preventative, maintenance and therapeutic methods were designed to be applied to the treatment of side effects elicited by either the exogenous administration of adenosine, of other agents which have unwanted adenosine-like effects described here, or of agents which elicit an endogenous release of adenosine. The agent of the invention may be administered either alone or with other therapeutic and diagnostic agents including adenosine, dipyrimidol, other adenosine receptor stimulants, adenosine releasing agents, etc. The present compositions and formulations for systemic and topical administration may be administered prior to, in conjunction with, or subsequent to the administration of adenosine or other adenosine receptor active agents.

The present inventors unexpectedly found that the agents of the invention, particularly those which have at least some inhibitory activity over the adenosine A₁ receptor, strongly inhibit, and in some cases terminate, with 100% efficacy, the ability of adenosine to cause bronchoconstriction in hyperresponsive airways. Experimental work, some of which is provided in the examples of this patent, has shown a complete interference with, and cessation of, adenosine's ability to cause bronchoconstriction and other unwanted side effects associated with its activity at the adenosine receptor(s) in each of two animal models of human bronchial hyper-responsiveness: a hyper-responsive rabbit model and a hyperresponsive cynamologous monkey model, both being widely acknowledged by the scientific community as models for adenosine hyper-responsiveness in humans. The agents of this invention, therefore, have been shown to prevent the untoward side effects of adenosine in the hyper-responsive lung mediated via an adenosine A₁ receptor. The suppression of adenosine side effects seen upon the agent's administration is clearly applicable to the treatment of hyper-sensitized subjects jointly with adenosine or by itself, either prior to, simultaneously with, and subsequent to adenosine administration to SVT afflicted subjects. In addition, the present agents are also effective for administration to subjects who need to undergo an adenosine stress test but who, prior to this invention, were prevented from the benefits associated with the administration of such test. The present agent now permits the free administration of adenosine or adenosine-like agents to persons with asthma and other respiratory diseases by preventing or alleviating the bronchial, allergic and/or inflammatory side effects produced by them.

To summarize, adenosine is a natural nucleoside which is used in the treatment of paroxysmal supraventricular tachycardia (PSVT or SVT), including SVT associated with Wolff-Parkinson-White

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Syndrome, and as a pharmacologic means to evaluate cardiovascular health via an adenosine stress test. Many SVT patients and candidates for adenosine stress testing have hyper-responsive airways associated with the over-expression of adenosine receptors, particularly the adenosine A_1 receptor. When activated by adenosine, the A_1 receptor may cause life threatening, and in some cases even fatal, bronchoconstriction in hyper-responsive airways. The present invention, therefore, permits therapeutic and diagnostic uses of adenosine in subjects whose health and well being would have been previously threatened by administration of adenosine, such as asthmatics and those afflicted by other conditions associated with hyper-responsiveness to this compound.

One of the present agents, i.e. Oligo I (SEQ. ID NO:1; EPI 2010) was shown to be effective in single-handedly eliminating with virtually 100% efficacy the ability of adenosine to cause bronchoconstriction in hyper-responsive airways. The complete termination of the ability of adenosine to cause bronchoconstriction is shown in the exemplary disclosure in two animal models of human bronchial hyper-responsiveness: the hyper-responsive rabbit and the hyper-responsive cynamologous monkey. The oligos of this invention, therefore, are suitable for preventing untoward side effects of adenosine administration in the hyper-responsive lung.

As used herein, the terms "prevent", "preventing", "treat" or "treating" refer to a preventative or therapeutic treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms associated with adenosine receptor stimulation. The term "down-regulate" refers to inducing a decrease in production, secretion or availability and, thus, a decrease in concentration, of intracellular adenosine A₁, A_{2b} or A₃ receptor or an increase in concentration of the adenosine A_{2a} receptor. Also suitable is the use of A2a agonists. Although the present invention is primarily concerned with the treatment of human subjects, it is also applicable to the treatment of animals, such as other vertebrates, including mammals, large and small, wild and domesticated, including pets, e.g. dogs and cats, for veterinary purposes. In general, "anti-sense" refers to small, many times synthetic, oligonucleotides, resembling single-stranded DNA, targeted to a specific gene, its flanking regions, mRNA or protein encoded by the gene and mRNA, which may be utilized for inhibiting gene expression by inhibiting the function of the target messenger RNA (mRNA). Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993). The present invention, thus, is intended for inhibiting gene expression of the adenosine A₁, A_{2b} or A₃ receptor as well as for promoting the gene expression of the adenosine A_{2a} receptor. As is generally known in the art, the inhibition of gene expression may be I brought about through anti-sense oligonucleotide hybridization to the coding (sense) sequences in a specific messenger RNA (mRNA) target, e.g. by hydrogen bonding according to Watson-Crick base pairing rules. In general, the exogenously administered anti-sense oligos decrease the mRNA and protein levels of the target gene or cause changes in the growth characteristics or shapes of the cells. Ibid. See, also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049: 99-125 (1990); Cohen, J. S., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987). As used herein, "adenosine receptor anti-sense oligonucleotide (oligo)" is a short sequence of synthetic nucleotide that (1) hybridizes to any coding sequence in an mRNA which codes for an adenosine receptor, e.g., the adenosine A₁, A_{2b} or A₃ receptor, under in vivo hybridization conditions described below, and that (2) upon hybridization causes a decrease in gene expression of the adenosine A₁, A_{2b} or

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 A_3 receptor. As used in this patent an adenosine A_{2a} agonist is any compound or agent that triggers an A_{2a} mediated agonist response or increases the level of A_{2a} receptor. As used in this patent, an adenosine A_{2a} agonist is any compound or agent that triggers an A_{2a} mediated agonist response or increases the level of A_{2a} receptor.

The mRNA sequence of the adenosine A_1 , A_{2a} , A_{2b} and A_3 receptors may be derived from the DNA base sequences of the genes expressing either the adenosine A_1 , A_{2b} and A_3 receptors. The sequence of the genomic human adenosine A_1 receptor is known and is disclosed in U.S. Patent No. 5,320,962 to G. Stiles et al. The adenosine A_{2b} receptor is also known. See, for example, GenBank, Accession No. X68486; GenBank Accession No. X68487. The adenosine A_3 receptor has been cloned, sequenced and expressed in rat and humans. See, F. Zhou et al., Proc. Nat'l. Acad. Sci. (USA) 89:7432 (1992); M.A. Jacobson et al., U.K. Patent Application No. 9304582.1 (1993). The anti-sense oligonucleotides that down-regulate the production of the adenosine A_{1b} , A_{2b} and A_{3} receptor and to upregulate the adenosine A_{2a} receptor may be produced in accordance with standard techniques. Adenosine A_{2a} agonists are known in the art and need not be listed here.

The agent of this invention binds specifically with any sequence of a mRNA molecule which is associated with or encodes an adenosine A_1 , A_{2a} , A_{2b} or A_3 receptor, and prevents translation of the mRNA molecule. In one embodiment of the present invention, the anti-sense oligonucleotide has one of the following sequences. In another preferred embodiment, the agent of the invention comprises fragments of these sequences or their combinations as well as sequences with decreased adenosine contents when compared with the natural sequences, where one or more adenosines are replaced by a universal base or adenosine analogue which does not activate adenosine receptors, particularly adenosine A_1 receptors.

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5'-GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)
5'-GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3)
5'-GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5)
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In still another embodiment, oligos that are anti-sense to the adenosine A_{2a} receptor and have agonistic activity and other adenosine A_{2a} receptor agents are used for the treatment of RDS and other respiratory problems in "preemies."

In another embodiment of the invention, the sequence of the anti-sense oligonucleotide brackets the initiation codon of the adenosine A₁ receptor, for example that of the human receptor mRNA. Preferred human adenosine A₁ receptor anti-sense oligonucleotide may have the SEQ. ID NO: 7 or any one of its fragments, including one of the following sequences. In another preferred embodiment, fragments of these sequences and/or their combinations are also within the confines of the invention.

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5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(SEQ. ID NO:7),
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'(Fragment 1) (SEQ. ID NO:8) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'(Fragment 2) (SEQ. ID NO:9)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'(Fragment 3) (SEQ. ID NO:10) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 4) (SEQ. ID NO:11)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 5) (SEQ. ID NO:12)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 7) (SEQ. ID NO:13)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 7) (SEQ. ID NO:14)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 8) (SEQ. ID NO:15)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 9) (SEQ. ID NO:16)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 10) (SEQ. ID NO:16)
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5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 11) (SEO, ID NO:18)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 12) (SEO. ID NO:19)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 13) (SEQ. ID NO:20)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 14) (SEQ. ID NO:21)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 15) (SEQ. ID NO:22)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 16) (SEQ. ID NO:23) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 17) (SEQ. ID NO:24)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 18) (SEQ. ID NO:25)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 19) (SEQ. ID NO:26)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 20) (SEQ. ID NO:27)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 21) (SEQ. 1D NO:28)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 22) (SEQ. ID NO:29)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 23) (SEO. ID NO:30)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 24) (SEQ. ID NO:31)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 25) (SEQ. 1D NO:32)
5'-GGC GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 26) (SEO. ID NO:33)
5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 27) (SEQ. ID NO:34)
5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (Fragment 28) (SEQ. ID NO:35)
5'-GGC GGC CTG GAA AGC TGA GAT G -3' (Fragment 29) (SEQ. ID NO:36) 5'-GGC GGC CTG GAA AGC TGA GAT -3' (Fragment 30) (SEQ. ID NO:37)
5'-GGC GGC CTG GAA AGC TGA GA-3' (Fragment 31) (SEQ. ID NO:38)
5'-GGC GGC CTG GAA AGC TGA G-3' (Fragment 32) (SEQ. ID NO:39)
5'-GGC GGC CTG GAA AGC TGA-3' (Fragment 33) (SEQ. ID NO:40)
5'-GGC GGC CTG GAA AGC TG-3' (Fragment 34) (SEQ. ID NO:41)
5'-GGC GGC CTG GAA AGC T-3 ' (Fragment 35) (SEQ. ID NO:42) 5'-GGC GGC CTG GAA AGC-3' (Fragment 36) (SEQ. ID NO:43)
5'-GGC GGC CTG GAA AG-3' (Fragment 37) (SEQ. ID NO:44)
5'-GGC GGC CTG GAA A-3' (Fragment 38) (SEO. ID NO:45)
5'-GGC GGC CTG GAA-3' (Fragment 39) (SEQ. ID NO:46)
5'-GGC GGC CTG GA-3' (Fragment 40) (SEQ. ID NO:47)
5'-GGC GGC CTG G-3' (Fragment 41) (SEQ. ID NO:48)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
(Fragment 42) (SEQ. ID NO:49)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
(Fragment 43) (SEQ. ID NO:50)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
(Fragment 44) (SEQ. ID NO:51)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'
(Fragment 45) (SEQ. ID NO:52)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 46) (SEQ. ID NO:53)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 47) (SEQ. ID NO:54)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 48) (SEQ. ID NO:55)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 49) (SEQ. ID NO:56) 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 50) (SEQ. ID NO:57)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 51) (SEQ. ID NO:58)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 52) (SEQ. ID NO:59)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 53) (SEQ. ID NO:60)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 54) (SEO. ID NO:61)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 55) (SEQ. ID NO:62)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 56) (SEQ. ID NO:63)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 57) (SEQ. ID NO:64)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 58) (SEQ. ID NO:65)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 59) (SEQ. ID NO:66)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 60) (SEO. ID NO:67)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 61) (SEQ. ID NO:68)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 62) (SEQ. ID NO:69)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 63) (SEQ. ID NO:70)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 64) (SEQ. ID NO:71)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 65) (SEQ. ID NO:72)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 66) (SEQ. ID NO:73)
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 67) (SEQ. ID NO:74)
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 68) (SEQ. ID NO:75)
5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 69) (SEQ. ID NO:76)
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (Fragment 70) (SEQ. ID NO:77)
5'-GC GGC CTG GAA AGC TGA GAT G -3' (Fragment 71) (SEQ. ID NO:78)
5'-GC GGC CTG GAA AGC TGA GAT -3' (Fragment 72) (SEQ. ID NO:79)
5'-GC GGC CTG GAA AGC TGA GA-3' (Fragment 73) (SEQ. ID NO:80)
5'-GC GGC CTG GAA AGC TGA G-3' (Fragment 74) (SEQ. ID NO:81)
5'-GC GGC CTG GAA AGC TGA-3' (Fragment 75) (SEQ. ID NO:82)
5'-GC GGC CTG GAA AGC TG-3' (Fragment 76) (SEQ. ID NO:83)
5'-GC GGC CTG GAA AGC T-3' (Fragment 77) (SEQ. ID NO:84)
5'-GC GGC CTG GAA AGC-3' (Fragment 78) (SEQ. ID NO:85)
5'-GC GGC CTG GAA AG-3' (Fragment 79) (SEQ. ID NO:86)
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5'-GC GGC CTG GAA A-3' (Fragment 80) (SEQ. ID NO:87)
 5'-GC GGC CTG GAA-3' (Fragment 81) (SEO, ID NO:88)
 5'-GC GGC CTG GA-3' (Fragment 82) (SEQ. ID NO:89)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
 (Fragment 83) (SEQ. ID NO:90)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3
 '(Fragment 84) (SEQ. ID NO:91)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
 (Fragment 85) (SEQ. ID NO:92)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'(Fragment 86) (SEQ. ID NO:93)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 87) (SEQ. ID NO:94)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 88) (SEQ. ID NO:95)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 89) (SEQ. ID NO:96) 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 90) (SEQ. ID NO:97)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 91) (SEQ. ID NO:98)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 92) (SEQ. ID NO:99)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 93) (SEQ. ID NO:100)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 94) (SEQ. ID NO:101)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 95) (SEQ. ID NO:102)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 96) (SEQ. ID NO:103)
 5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 97) (SEQ. ID NO:104)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 98) (SEQ. ID NO:105)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 99) (SEQ. ID NO:106)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 100) (SEQ. ID NO:107)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 101) (SEQ. ID NO:108)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 102) (SEQ. ID NO:109)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 103) (SEQ. ID NO:110)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 104) (SEQ. ID NO:111)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 105) (SEQ. ID NO:112)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 106) (SEQ. ID NO:113)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 107) (SEQ. ID NO:114)
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 108) (SEQ. ID NO:115)
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 109) (SEQ. ID NO:116)
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 110) (SEQ. ID NO:117)
5'-C GGC CTG GAA AGC TGA GAT GG -3' (Fragment 111) (SEQ. ID NO:118)
5'-C GGC CTG GAA AGC TGA GAT G -3' (Fragment 112) (SEQ. ID NO:119)
5'-C GGC CTG GAA AGC TGA GAT -3' (Fragment 113) (SEQ. ID NO:120)
5'-C GGC CTG GAA AGC TGA GA-3' (Fragment 114) (SEQ. ID NO:121)
5'-C GGC CTG GAA AGC TGA G-3' (Fragment 115) (SEQ. ID NO:122)
5'-C GGC CTG GAA AGC TGA-3' (Fragment 116) (SEQ. ID NO:123)
5'-C GGC CTG GAA AGC TG-3' (Fragment 117) (SEQ. ID NO:124)
5'-C GGC CTG GAA AGC T-3' (Fragment 118) (SEQ. ID NO:125)
5'-C GGC CTG GAA AGC-3' (Fragment 119) (SEQ. ID NO:126)
5'-C GGC CTG GAA AG-3' (Fragment 120) (SEQ. ID NO:127)
5'-C GGC CTG GAA A-3' (Fragment 121) (SEQ. ID NO:128)
5'-C GGC CTG GAA-3' (Fragment 122) (SEQ. ID NO:129)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
(Fragment 123) (SEQ. ID NO:130)
5'- GGC CTG GAA ÀGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
(Fragment 124) (SEQ. ID NO:131)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
(Fragment 125) (SEQ. ID NO:132)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3 (Fragment 126) (SEQ. ID NO:133)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 127) (SEQ. ID NO:134)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 128) (SEQ. ID NO:135)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 129) (SEQ. ID NO:136)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 130) (SEQ. ID NO:137)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 131) (SEQ. ID NO:138)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 132) (SEQ. ID NO:139)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3'(Fragment 133) (SEQ. ID NO:140)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 134) (SEQ. ID NO:141)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 135) (SEQ. ID NO:142) 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 136) (SEQ. ID NO:143)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 137) (SEQ. ID NO:144) 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 138) (SEQ. ID NO:145)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 139) (SEQ. ID NO:146)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 140) (SEQ. ID NO:147)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 141) (SEQ. ID NO:148)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 142) (SEQ. ID NO:149)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 143) (SEQ. ID NO:150)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 144) (SEQ. ID NO:151)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 145) (SEQ. ID NO:152)
5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 146) (SEQ. ID NO:153)
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5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 147) (SEQ. ID NO:154)
 5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 148) (SEQ. ID NO:155)
 5'- GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 149) (SEQ. ID NO:156) 5'- GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 150) (SEQ. ID NO:157)
 5'- GGC CTG GAA AGC TGA GAT GG -3' (Fragment 151) (SEQ. ID NO:158)
 5'- GGC CTG GAA AGC TGA GAT G -3' (Fragment 152) (SEQ. ID NO:159)
5'- GGC CTG GAA AGC TGA GAT -3' (Fragment 153) (SEQ. ID NO:160)
 5'- GGC CTG GAA AGC TGA GA-3' (Fragment 154) (SEQ. ID NO:161)
 5'- GGC CTG GAA AGC TGA G-3' (Fragment 155) (SEQ. ID NO:162)
5'- GGC CTG GAA AGC TGA-3' (Fragment 156) (SEQ. ID NO:163)
 5'- GGC CTG GAA AGC TG-3' (Fragment 157) (SEQ. ID NO:164)
 5'- GGC CTG GAA AGC T-3' (Fragment 158) (SEQ. ID NO:165)
 5'- GGC CTG GAA AGC-3' (Fragment 159) (SEQ. ID NO:166)
 5'- GGC CTG GAA AG-3' (Fragment 160) (SEQ. ID NO:167)
 5'- GGC CTG GAA A-3' (Fragment 161) (SEQ. ID NO:168)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
 (Fragment 162) (SEQ. ID NO:169)
 5'- GC CTG GÁA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
(Fragment 163) (SEQ. ID NO:170)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 164) (SEQ. ID NO:171) 5'- GC CTG
 GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 165) (SEQ. ID NO:172)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 166) (SEQ. ID NO:173)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 167) (SEQ. ID NO:174)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 168) (SEQ. 1D NO:175)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 169) (SEQ. ID NO:176)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 170) (SEQ. ID NO:177)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 171) (SEQ. ID NO:178)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 172) (SEQ. ID NO:179)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 173) (SEQ. ID NO:180)
 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 174) (SEQ. ID NO:181)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 175) (SEQ. ID NO:182)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 176) (SEQ. ID NO:183)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 177) (SEQ. ID NO:184)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 178) (SEQ. ID NO:185)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 179) (SEQ. ID NO:186)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 180) (SEQ. ID NO:187)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 181) (SEQ. ID NO:188)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 182) (SEQ. ID NO:189)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 183) (SEQ. ID NO:190)
5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 184) (SEQ. ID NO:191)
5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 185) (SEQ. ID NO:192)
5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 186) (SEQ. ID NO:193)
5'- GC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 187) (SEQ. ID NO:194)
5'- GC CTG GAA AGC TGA GAT GGA G -3' (Fragment 188) (SEQ. ID NO:195)
5'- GC CTG GAA AGC TGA GAT GGA -3' (Fragment 189) (SEQ. ID NO:196)
5'- GC CTG GAA AGC TGA GAT GG -3' (Fragment 190) (SEQ. ID NO:197)
5'- GC CTG GAA AGC TGA GAT G -3' (Fragment 191) (SEQ. ID NO:198)
5'- GC CTG GAA AGC TGA GAT -3' (Fragment 192) (SEQ. ID NO:199)
5'- GC CTG GAA AGC TGA GA-3' (Fragment 193) (SEQ. ID NO:200)
5'- GC CTG GAA AGC TGA G-3' (Fragment 194) (SEQ. ID NO:201)
5'- GC CTG GAA AGC TGA-3' (Fragment 195) (SEQ. ID NO:202)
5'- GC CTG GAA AGC TG-3' (Fragment 196) (SEQ. ID NO:203)
5'- GC CTG GAA AGC T-3' (Fragment 197) (SEQ. ID NO:204)
5'- GC CTG GAA AGC-3' (Fragment 198) (SEQ. ID NO:205)
5'- GC CTG GAA AG-3' (Fragment 199) (SEQ. ID NO:206)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 200) (SEQ. ID NO:207)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 201) (SEQ. ID NO:208) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 202) (SEQ. ID NO:209)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 203) (SEQ. ID NO:210)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3'(Fragment 204) (SEQ. ID NO:211)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 205) (SEQ. ID NO:212)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 206) (SEQ. ID NO:213)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 207) (SEQ. ID NO:214)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 208) (SEQ. ID NO:215)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 209) (SEQ. ID NO:216) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 210) (SEQ. ID NO:217)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 211) (SEQ. ID NO:218)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 212) (SEQ. ID NO:219)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 213) (SEQ. ID NO:220)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 214) (SEQ. ID NO:221)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 215) (SEQ. ID NO:222)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 216) (SEQ. ID NO:223)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 217) (SEQ. ID NO:224)
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5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 218) (SEQ. ID NO:225)
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 219) (SEQ. 1D NO:226)
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 220) (SEQ. ID NO:227)
 5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 221) (SEQ. ID NO:228)
 5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 222) (SEQ. ID NO:229)
 5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 223) (SEQ. ID NO:230)
 5'- C CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 224) (SEQ. ID NO:231)
 5'- C CTG GAA AGC TGA GAT GGA GG -3' (Fragment 225) (SEQ. ID NO:232)
 5'- C CTG GAA AGC TGA GAT GGA G -3' (Fragment 226) (SEQ. ID NO:233)
 5'- C CTG GAA AGC TGA GAT GGA -3' (Fragment 227) (SEQ. ID NO:234)
5'- C CTG GAA AGC TGA GAT GG -3' (Fragment 228) (SEQ. ID NO:235)
 5'- C CTG GAA AGC TGA GAT G -3' (Fragment 229) (SEQ. ID NO:236)
 5'- C CTG GAA AGC TGA GAT -3' (Fragment 230) (SEQ. ID NO:237)
5'- C CTG GAA AGC TGA GA-3' (Fragment 231) (SEQ. ID NO:238)
 5'- C CTG GAA AGC TGA G-3' (Fragment 232) (SEQ. ID NO:239)
5'- C CTG GAA AGC TGA-3' (Fragment 233) (SEQ. ID NO:240)
5'- C CTG GAA AGC TG-3' (Fragment 234) (SEQ. ID NO:241)
 5'- C CTG GAA AGC T-3' (Fragment 235) (SEQ. ID NO:242)
 5'- C CTG GAA AGC-3' (Fragment 236) (SEQ. ID NO:243)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 237) (SEQ. ID NO:244) 5'- CTG GAA
AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 238) (SEQ. ID NO:245)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 239) (SEQ. ID NO:246)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 240) (SEQ. ID NO:247) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 241) (SEQ. ID NO:248)
 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 242) (SEQ. ID NO:249)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 243) (SEQ. ID NO:250)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 244) (SEQ. ID NO:251)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 245) (SEQ. ID NO:252)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 246) (SEQ. ID NO:253)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 247) (SEQ. ID NO:254)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 248) (SEQ. ID NO:255)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 249) (SEQ. ID NO:256)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 250) (SEQ. ID NO:257)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 251) (SEQ. ID NO:258)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 252) (SEQ. ID NO:259)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 253) (SEQ. ID NO:260)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 254) (SEQ. ID NO:261)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 255) (SEQ. ID NO:262)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 256) (SEQ. ID NO:263)
5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 257) (SEQ. ID NO:264)
5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 258) (SEQ. 1D NO:265)
5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 259) (SEQ. ID NO:266)
5'- CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 260) (SEQ. ID NO:267)
5'- CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 261) (SEQ. ID NO:268)
5'- CTG GAA AGC TGA GAT GGA GG -3' (Fragment 262) (SEQ. ID NO:269)
5'- CTG GAA AGC TGA GAT GGA G -3' (Fragment 263) (SEQ. ID NO:270)
5'- CTG GAA AGC TGA GAT GGA -3' (Fragment 264) (SEQ. ID NO:271)
5'- CTG GAA AGC TGA GAT GG -3' (Fragment 265) (SEQ. ID NO:272)
5'- CTG GAA AGC TGA GAT G -3' (Fragment 266) (SEQ. ID NO:273)
5'- CTG GAA AGC TGA GAT -3' (Fragment 267) (SEQ. ID NO:274)
5'- CTG GAA AGC TGA GA-3' (Fragment 268) (SEQ. ID NO:275)
5'- CTG GAA AGC TGA G-3' (Fragment 269) (SEQ. ID NO:276)
5'- CTG GAA AGC TGA-3' (Fragment 270) (SEO. ID NO:277)
5'- CTG GAA AGC TG-3' (Fragment 271) (SEQ. ID NO:278)
5'- CTG GAA AGC T-3' (Fragment 272) (SEQ. ID NO:279)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 273) (SEQ. ID NO:280)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 274) (SEQ. ID NO:281)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 275) (SEQ. ID NO:282)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 276) (SEQ. ID NO:283)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 277) (SEQ. ID NO:284)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 278) (SEQ. ID NO:285)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 279) (SEQ. ID NO:286)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 280) (SEQ. ID NO:287)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 281) (SEQ. ID NO:288)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 282) (SEQ. ID NO:289)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 283) (SEQ. ID NO:290)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 284) (SEQ. ID NO:291)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 285) (SEQ. ID NO:292)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 286) (SEQ. ID NO:293)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 287) (SEQ. ID NO:294)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 288) (SEQ. ID NO:295)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 289) (SEQ. ID NO:296)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 290) (SEQ. ID NO:297)
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5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 291) (SEQ. ID NO:298)
5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 292) (SEQ. ID NO:299)
5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 293) (SEQ. ID NO:300)
5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 294) (SEQ. ID NO:301)
5'- TG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 295) (SEO. ID NO:302)
5'- TG GAA AGC TGA GAT GGA GGG C-3' (Fragment 296) (SEO. ID NO:303)
5'- TG GAA AGC TGA GAT GGA GGG -3' (Fragment 297) (SEQ. ID NO:304)
5'- TG GAA AGC TGA GAT GGA GG -3' (Fragment 298) (SEQ. ID NO:305)
5'- TG GAA AGC TGA GAT GGA G -3' (Fragment 299) (SEQ. ID NO:306)
5'- TG GAA AGC TGA GAT GGA -3' (Fragment 300) (SEQ. ID NO:307)
5'- TG GAA AGC TGA GAT GG -3' (Fragment 301) (SEQ. ID NO:308)
5'- TG GAA AGC TGA GAT G -3' (Fragment 302) (SEQ. ID NO:309)
5'- TG GAA AGC TGA GAT -3' (Fragment 303) (SEQ. ID NO:310)
5'- TG GAA AGC TGA GA-3' (Fragment 304) (SEQ. ID NO:311)
5'- TG GAA AGC TGA G-3' (Fragment 305) (SEQ. ID NO:312)
5'- TG GAA AGC TGA-3' (Fragment 306) (SEQ. ID NO:313)
5'- TG GAA AGC TG-3' (Fragment 307) (SEQ. ID NO:314)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 308) (SEQ. ID NO:315)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'(Fragment 309) (SEQ. ID NO:316)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 310) (SEQ. ID NO:317)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 311) (SEQ. ID NO:318) 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 312) (SEQ. ID NO:319)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 313) (SEQ. ID NO:320)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 314) (SEQ. ID NO:321)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 315) (SEO. ID NO:322)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 316) (SEQ. ID NO:323)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 317) (SEQ. ID NO:324)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 318) (SEQ. ID NO:325)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 319) (SEQ. ID NO:326)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 320) (SEQ. ID NO:327)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG -3' (Fragment 321) (SEQ. ID NO:328)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 322) (SEQ. ID NO:329)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3 (Fragment 323) (SEQ. ID NO:330)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 324) (SEQ. ID NO:331)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 325) (SEQ. ID NO:332)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 326) (SEQ. ID NO:333)
5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 327) (SEO. ID NO:334)
5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 328) (SEQ. ID NO:335)
5'- G GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 329) (SEQ. ID NO:336)
5'- G GAA AGC TGA GAT GGA GGG CG -3' (Fragment 330) (SEQ. ID NO:337)
5'- G GAA AGC TGA GAT GGA GGG C -3' (Fragment 331) (SEQ. ID NO:338)
5'- G GAA AGC TGA GAT GGA GGG -3' (Fragment 332) (SEQ. ID NO:339)
5'- G GAA AGC TGA GAT GGA GG -3' (Fragment 333) (SEQ. ID NO:340)
5'- G GAA AGC TGA GAT GGA G -3' (Fragment 334) (SEQ. ID NO:341)
5'- G GAA AGC TGA GAT GGA -3' (Fragment 335) (SEQ. ID NO:342)
5'- G GAA AGC TGA GAT GG -3' (Fragment 336) (SEQ. ID NO:343)
5'- G GAA AGC TGA GAT G -3' (Fragment 337) (SEQ. ID NO:344)
5'- G GAA AGC TGA GAT -3' (Fragment 338) (SEQ. ID NO:345)
5'- G GAA AGC TGA GA-3' (Fragment 339) (SEQ. ID NO:346)
5'- G GAA AGC TGA G-3' (Fragment 340) (SEQ. ID NO:347)
5'- G GAA AGC TGA-3' (Fragment 341) (SEQ. ID NO:348)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 342) (SEQ. ID NO:349)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 343) (SEQ. ID NO:350)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 344) (SEQ. ID NO:351)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 345) (SEQ. ID NO:352)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 346) (SEQ. ID NO:353)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 347) (SEQ. ID NO:354)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 348) (SEQ. ID NO:355)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 349) (SEQ. ID NO:356)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 350) (SEQ. ID NO:357)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 351) (SEQ. 1D NO:358)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 352) (SEQ. ID NO:359)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 353) (SEQ. ID NO:360)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 354) (SEQ. ID NO:361)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 355) (SEQ. ID NO:362)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 356) (SEQ. ID NO:363)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 357) (SEQ. ID NO:364)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 358) (SEQ. ID NO:365)
5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 359) (SEQ. 1D NO:366)
5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 360) (SEQ. ID NO:367)
5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 361) (SEQ. ID NO:368)
5'- GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 362) (SEQ. ID NO:369)
5'- GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 363) (SEQ. 1D NO:370)
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5'- GAA AGC TGA GAT GGA GGG CG -3' (Fragment 364) (SEQ. ID NO:371)
5'- GAA AGC TGA GAT GGA GGG C -3' (Fragment 365) (SEO, ID NO:372)
5'- GAA AGC TGA GAT GGA GGG -3' (Fragment 366) (SEQ. ID NO:373)
5'- GAA AGC TGA GAT GGA GG -3' (Fragment 367) (SEQ. ID NO:374)
5'- GAA AGC TGA GAT GGA G -3' (Fragment 368) (SEQ. ID NO:375)
5'- GAA AGC TGA GAT GGA -3' (Fragment 369) (SEQ. ID NO:376)
5'- GAA AGC TGA GAT GG -3' (Fragment 370) (SEQ. ID NO:377)
5'- GAA AGC TGA GAT G -3' (Fragment 371) (SEQ. ID NO:378)
5'- GAA AGC TGA GAT -3' (Fragment 372) (SEQ. ID NO:379)
5'- GAA AGC TGA GA-3' (Fragment 373) (SEQ. ID NO:380)
5'- GAA AGC TGA G-3' (Fragment 374) (SEQ. ID NO:381)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 375) (SEQ. ID NO:382)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 376) (SEQ. ID NO:383)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 377) (SEQ. ID NO:384)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 378) (SEO. ID NO:385)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 379) (SEQ. ID NO:386)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 380) (SEQ. ID NO:387)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 381) (SEQ. ID NO:388)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 382) (SEQ. ID NO:389)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 383) (SEQ. ID NO:390)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 384) (SEQ. ID NO:391)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 385) (SEQ. ID NO:392)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 386) (SEQ. ID NO:393)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 387) (SEQ. ID NO:394)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 388) (SEQ. ID NO:395)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 389) (SEQ. ID NO:396)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 390) (SEQ. ID NO:397)
5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 391) (SEQ. ID NO:398)
5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 392) (SEQ. ID NO:399)
5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 393) (SEQ. ID NO:400)
5'- AA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 394) (SEQ. ID NO:401)
5'- AA AGC TGA GAT GGA GGG CGG C-3' (Fragment 395) (SEQ. ID NO:402)
   AA AGC TGA GAT GGA GGG CGG -3' (Fragment 396) (SEQ. ID NO:403)
   AA AGC TGA GAT GGA GGG CG -3' (Fragment 397) (SEQ. ID NO:404)
5'- AA AGC TGA GAT GGA GGG C -3' (Fragment 398) (SEQ. ID NO:405)
5'- AA AGC TGA GAT GGA GGG -3' (Fragment 399) (SEQ. ID NO:406)
   AA AGC TGA GAT GGA GG -3' (Fragment 400) (SEQ. ID NO:407)
5'- AA AGC TGA GAT GGA G -3' (Fragment 401) (SEQ. ID NO:408)
5'- AA AGC TGA GAT GGA -3' (Fragment 402) (SEQ. ID NO:409)
5'- AA AGC TGA GAT GG -3' (Fragment 403) (SEQ. ID NO:410)
5'- AA AGC TGA GAT G -3' (Fragment 404) (SEQ. ID NO:411)
5'- AA AGC TGA GAT -3' (Fragment 405) (SEQ. ID NO:412)
5'- AA AGC TGA GA-3' (Fragment 406) (SEQ. ID NO:413)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 407) (SEQ. ID NO:414)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 408) (SEQ. ID NO:415)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 409) (SEQ. ID NO:416)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 410) (SEQ. ID NO:417)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 411) (SEQ. ID NO:418)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 412) (SEO, ID NO:419)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 413) (SEQ. ID NO:420)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 414) (SEQ. ID NO:421)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 415) (SEO. ID NO:422)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 416) (SEQ. ID NO:423)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 417) (SEQ. ID NO:424)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 418) (SEO. ID NO:425)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 419) (SEQ. ID NO:426)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 420) (SEQ. ID NO:427)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 421) (SEO. ID NO:428)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 422) (SEQ. ID NO:429)
5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 423) (SEQ. ID NO:430)
5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 424) (SEO, ID NO:431)
5'- A AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 425) (SEQ. ID NO:432)
5'- A AGC TGA GAT GGA GGG CGG CA-3' (Fragment 426) (SEQ. ID NO:433)
5'- A AGC TGA GAT GGA GGG CGG C-3' (Fragment 427) (SEO, ID NO:434)
5'- A AGC TGA GAT GGA GGG CGG -3' (Fragment 428) (SEQ. ID NO:435)
5'- A AGC TGA GAT GGA GGG CG -3' (Fragment 429) (SEQ. ID NO:436)
5'- A AGC TGA GAT GGA GGG C -3' (Fragment 430) (SEO, ID NO:437)
5'- A AGC TGA GAT GGA GGG -3' (Fragment 431) (SEQ. ID NO:438)
5'- A AGC TGA GAT GGA GG -3' (Fragment 432) (SEQ. ID NO:439)
5'- A AGC TGA GAT GGA G -3' (Fragment 433) (SEQ. ID NO:440)
5'- A AGC TGA GAT GGA -3' (Fragment 434) (SEQ. ID NO:441)
5'- A AGC TGA GAT GG -3' (Fragment 435) (SEQ. ID NO:442)
5'- A AGC TGA GAT G -3' (Fragment 436) (SEQ. ID NO:443)
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5'- A AGC TGA GAT -3' (Fragment 437) (SEQ. ID NO:444)
   AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 438) (SEQ. ID NO:445)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 439) (SEQ. ID NO:446)
5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 440) (SEO. ID NO:447)
   AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 441) (SEQ. ID NO:448)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 442) (SEQ. ID NO:449)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 443) (SEQ. ID NO:450)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 444) (SEQ. ID NO:451)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 445) (SEQ. ID NO:452)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 446) (SEO, ID NO:453)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 447) (SEO. ID NO:454)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 448) (SEQ. ID NO:455)
5'-
    AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 449) (SEQ. 1D NO:456)
    AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 450) (SEQ. ID NO:457)
5'-
    AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 451) (SEQ. ID NO:458)
    AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 452) (SEQ. ID NO:459)
    AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 453) (SEQ. ID NO:460)
5'-
    AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 454) (SEQ. ID NO:461)
    AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 455) (SEQ. ID NO:462) AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 456) (SEQ. ID NO:463)
5'-
    AGC TGA GAT GGA GGG CGG CA-3' (Fragment 457) (SEO. ID NO:464)
    AGC TGA GAT GGA GGG CGG C-3' (Fragment 458) (SEQ. ID NO:465)
AGC TGA GAT GGA GGG CGG -3' (Fragment 459) (SEQ. ID NO:466)
    AGC TGA GAT GGA GGG CG -3' (Fragment 460) (SEQ. ID NO:467)
    AGC TGA GAT GGA GGG C -3' (Fragment 461) (SEQ. ID NO:468)
    AGC TGA GAT GGA GGG -3' (Fragment 462) (SEQ. ID NO:469)
    AGC TGA GAT GGA GG -3' (Fragment 463) (SEQ. ID NO:470)
    AGC TGA GAT GGA G -3' (Fragment 464) (SEQ. ID NO:471)
AGC TGA GAT GGA -3' (Fragment 465) (SEQ. ID NO:472)
    AGC TGA GAT GG -3' (Fragment 466) (SEO. ID NO:473)
    AGC TGA GAT G -3' (Fragment 467) (SEQ. ID NO:474)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 468) (SEQ. ID NO:475)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 469) (SEQ. ID NO:476)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 470) (SEQ. ID NO:477)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 471) (SEQ. ID NO:478)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 472) (SEQ. ID NO:479)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 473) (SEQ. ID NO:480)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 474) (SEQ. ID NO:481)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 475) (SEO. ID NO:482)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 476) (SEQ. ID NO:483)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 477) (SEQ. ID NO:484)
    GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 478) (SEQ. ID NO:485)
    GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 479) (SEQ. ID NO:486)
    GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 480) (SEQ. ID NO:487)
    GC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 481) (SEQ. ID NO:488)
    GC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 482) (SEQ. ID NO:489)
    GC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 483) (SEQ. ID NO:490)
    GC TGA GAT GGA GGG CGG CAT GG -31 (Fragment 484) (SEQ. ID NO:491)
    GC TGA GAT GGA GGG CGG CAT G -3' (Fragment 485) (SEQ. ID NO:492)
    GC TGA GAT GGA GGG CGG CAT -3' (Fragment 486) (SEQ. ID NO:493)
    GC TGA GAT GGA GGG CGG CA-3' (Fragment 487) (SEQ. ID NO:494)
    GC TGA GAT GGA GGG CGG C-3' (Fragment 488) (SEQ. 1D NO:495)
    GC TGA GAT GGA GGG CGG -3' (Fragment 489) (SEQ. ID NO:496)
    GC TGA GAT GGA GGG CG -3' (Fragment 490) (SEQ. ID NO:497)
    GC TGA GAT GGA GGG C -3' (Fragment 491) (SEQ. ID NO:498)
5'-
    GC TGA GAT GGA GGG -3' (Fragment 492) (SEQ. ID NO:499)
    GC TGA GAT GGA GG -3' (Fragment 493) (SEQ. ID NO:500)
    GC TGA GAT GGA G -3' (Fragment 494) (SEQ. ID NO:501)
    GC TGA GAT GGA -3' (Fragment 495) (SEQ. ID NO:502)
    GC TGA GAT GG -3' (Fragment 496) (SEQ. ID NO:503)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 497) (SEO, ID NO:504)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 498) (SEQ. ID NO:505) C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 499) (SEQ. ID NO:506)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 500) (SEO. ID NO:507)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 501) (SEQ. ID NO:508) C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 502) (SEQ. ID NO:509)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 503) (SEQ. 1D NO:510)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 504) (SEQ. ID NO:511)
C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 505) (SEQ. ID NO:512)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 506) (SEQ. ID NO:513)
    C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 507) (SEQ. ID NO:514)
    C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 508) (SEQ. ID NO:515)
    C TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 509) (SEQ. ID NO:516)
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5'- C TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 510) (SEQ. 1D NO:517)
    C TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 511) (SEQ. 1D NO:518)
    C TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 512) (SEQ. ID NO:519)
    C TGA GAT GGA GGG CGG CAT GG -3' (Fragment 513) (SEQ. ID NO:520)
    C TGA GAT GGA GGG CGG CAT G-3' (Fragment 514) (SEQ. ID NO:521)
    C TGA GAT GGA GGG CGG CAT -3' (Fragment 515) (SEQ. ID NO:522)
    C TGA GAT GGA GGG CGG CA-3' (Fragment 516) (SEQ. ID NO:523)
    C TGA GAT GGA GGG CGG C-3' (Fragment 517) (SEQ. ID NO:524)
    C TGA GAT GGA GGG CGG -3' (Fragment 518) (SEQ. ID NO:525)
    C TGA GAT GGA GGG CG -3' (Fragment 519) (SEQ. ID NO:526)
    C TGA GAT GGA GGG C -3' (Fragment 520) (SEQ. ID NO:527)
    C TGA GAT GGA GGG -3' (Fragment 521) (SEQ. ID NO:528)
    C TGA GAT GGA GG -3' (Fragment 522) (SEQ. ID NO:529)
    C TGA GAT GGA G -3' (Fragment 523) (SEQ. ID NO:530)
    C TGA GAT GGA -3' (Fragment 524) (SEQ. ID NO:531)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 525) (SEQ. ID NO:532)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 526) (SEQ. ID NO:533)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 527) (SEQ. ID NO:534)
5'-
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 528) (SEQ. ID NO:535)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 529) (SEQ. ID NO:536)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 530) (SEQ. ID NO:537)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 531) (SEQ. ID NO:538)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 532) (SEQ. 1D NO:539)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 533) (SEQ. ID NO:540)
    TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 534) (SEQ. ID NO:541)
5'-
    TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 535) (SEQ. ID NO:542)
    TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 536) (SEQ. ID NO:543)
5'-
    TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 537) (SEQ. ID NO:544)
    TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 538) (SEO. ID NO:545)
    TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 539) (SEQ. ID NO:546)
    TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 540) (SEQ. ID NO:547)
5'-
    TGA GAT GGA GGG CGG CAT GG -3' (Fragment 541) (SEQ. ID NO:548)
    TGA GAT GGA GGG CGG CAT G -3' (Fragment 542) (SEQ. ID NO:549)
    TGA GAT GGA GGG CGG CAT -3' (Fragment 543) (SEQ. ID NO:550)
5'-
    TGA GAT GGA GGG CGG CA-3' (Fragment 544) (SEQ. ID NO:551)
    TGA GAT GGA GGG CGG C-3' (Fragment 545) (SEQ. ID NO:552)
    TGA GAT GGA GGG CGG -3' (Fragment 546) (SEQ. ID NO:553)
5'-
    TGA GAT GGA GGG CG -3' (Fragment 547) (SEQ. ID NO:554)
    TGA GAT GGA GGG C -3' (Fragment 548) (SEQ. ID NO:555)
    TGA GAT GGA GGG -3' (Fragment 549) (SEQ. ID NO:556)
5'-
    TGA GAT GGA GG -3' (Fragment 550) (SEQ. ID NO:557)
    TGA GAT GGA G -3' (Fragment 551) (SEQ. ID NO:558)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 552) (SEQ. ID NO:559)
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    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 553) (SEQ. ID NO:560)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 554) (SEQ. ID NO:561)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 555) (SEQ. ID NO:562)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 556) (SEO. ID NO:563)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 557) (SEQ. ID NO:564)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 558) (SEQ. ID NO:565)
    GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 559) (SEQ. ID NO:566)
    GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 560) (SEQ. 1D NO:567)
    GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 561) (SEQ. ID NO:568)
    GA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 562) (SEQ. ID NO:569)
    GA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 563) (SEQ. ID NO:570)
    GA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 564) (SEQ. ID NO:571)
    GA GAT GGA GGG CGG CAT GGC GG-3! (Fragment 565) (SEQ. ID NO:572)
    GA GAT GGA GGG CGG CAT GGC G-3' (Fragment 566) (SEQ. ID NO:573)
    GA GAT GGA GGG CGG CAT GGC -3' (Fragment 567) (SEQ. ID NO:574)
    GA GAT GGA GGG CGG CAT GG -3' (Fragment 568) (SEQ. ID NO:575)
    GA GAT GGA GGG CGG CAT G -3' (Fragment 569) (SEQ. ID NO:576)
    GA GAT GGA GGG CGG CAT -3' (Fragment 570) (SEQ. ID NO:577)
    GA GAT GGA GGG CGG CA-3' (Fragment 571) (SEQ. ID NO:578)
5'-
    GA GAT GGA GGG CGG C-3' (Fragment 572) (SEQ. ID NO:579)
    GA GAT GGA GGG CGG -3' (Fragment 573) (SEQ. ID NO:580)
    GA GAT GGA GGG CG -3' (Fragment 574) (SEQ. ID NO:581)
    GA GAT GGA GGG C -3' (Fragment 575) (SEQ. ID NO:582)
    GA GAT GGA GGG -3' (Fragment 576) (SEQ. ID NO:583)
    GA GAT GGA GG -3' (Fragment 577) (SEQ. ID NO:584)
    A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 578) (SEQ. ID NO:585)
    A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 579) (SEQ. ID NO:586)
    A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 580) (SEQ. ID NO:587)
    A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 581) (SEQ. 1D NO:588)
    A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 582) (SEQ. ID NO:589)
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A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 583) (SEO. ID NO:590) 5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 584) (SEQ. ID NO:591) A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 585) (SEQ. ID NO:592) A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 586) (SEQ. ID NO:593) A GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 587) (SEQ. ID NO:594) A GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 588) (SEQ. ID NO:595) A GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 589) (SEQ. ID NO:596) A GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 590) (SEQ. 1D NO:597) A GAT GGA GGG CGG CAT GGC GG-3' (Fragment 591) (SEQ. ID NO:598) A GAT GGA GGG CGG CAT GGC G-3' (Fragment 592) (SEQ. ID NO:599) A GAT GGA GGG CGG CAT GGC -3' (Fragment 593) (SEQ. ID NO:600) A GAT GGA GGG CGG CAT GG -3' (Fragment 594) (SEQ. ID NO:601) A GAT GGA GGG CGG CAT G -3' (Fragment 595) (SEO, ID NO:602) A GAT GGA GGG CGG CAT -3' (Fragment 596) (SEQ. ID NO:603) A GAT GGA GGG CGG CA-3' (Fragment 597) (SEQ. ID NO:604) A GAT GGA GGG CGG C-3' (Fragment 598) (SEQ. ID NO:605) A GAT GGA GGG CGG -3' (Fragment 599) (SEQ. ID NO:606) A GAT GGA GGG CG -3' (Fragment 600) (SEQ. ID NO:607) A GAT GGA GGG C -3' (Fragment 601) (SEQ. ID NO:608) A GAT GGA GGG -3' (Fragment 602) (SEQ. ID NO:609) GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 603) (SEQ. ID NO:610) GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 604) (SEQ. ID NO:611) GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 605) (SEQ. ID NO:612) GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 606) (SEQ. ID NO:613) GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 607) (SEQ. ID NO:614) GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 608) (SEQ. ID NO:615) GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 609) (SEO, ID NO:616) GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 610) (SEQ. ID NO:617) GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 611) (SEQ. 1D NO:618) GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 612) (SEO. ID NO:619) GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 613) (SEQ. ID NO:620) GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 614) (SEQ. ID NO:621) GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 615) (SEO. ID NO:622) GAT GGA GGG CGG CAT GGC GG-3' (Fragment 616) (SEQ. ID NO:623) GAT GGA GGG CGG CAT GGC G-3' (Fragment 617) (SEQ. ID NO:624) GAT GGA GGG CGG CAT GGC -3' (Fragment 618) (SEO. ID NO:625) GAT GGA GGG CGG CAT GG -3' (Fragment 619) (SEQ. ID NO:626) GAT GGA GGG CGG CAT G -3' (Fragment 620) (SEQ. ID NO:627) GAT GGA GGG CGG CAT -3' (Fragment 621) (SEQ. ID NO:628) GAT GGA GGG CGG CA-3' (Fragment 622) (SEQ. ID NO:629) GAT GGA GGG CGG C-3' (Fragment 623) (SEQ. ID NO:630) GAT GGA GGG CGG -3' (Fragment 624) (SEQ. ID NO:631) GAT GGA GGG CG -3' (Fragment 625) (SEQ. ID NO:632) GAT GGA GGG C -3' (Fragment 626) (SEQ. ID NO:633) AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 627) (SEQ. ID NO:634) AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 628) (SEQ. ID NO:635) AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 629) (SEQ. ID NO:636) AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 630) (SEQ. ID NO:637) AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 631) (SEQ. ID NO:638) AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 632) (SEQ. ID NO:639) AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 633) (SEQ. ID NO:640) AT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 634) (SEQ. ID NO:641) AT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 635) (SEQ. ID NO:642) AT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 636) (SEQ. ID NO:643) AT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 637) (SEQ. ID NO:644) AT GGA GGG CGG CAT GGC GGG C-3' (Fragment 638) (SEO. ID NO:645) AT GGA GGG CGG CAT GGC GGG -3' (Fragment 639) (SEQ. ID NO:646) AT GGA GGG CGG CAT GGC GG-3' (Fragment 640) (SEQ. ID NO:647) AT GGA GGG CGG CAT GGC G-3' (Fragment 641) (SEO. ID NO:648) AT GGA GGG CGG CAT GGC -3' (Fragment 642) (SEQ. ID NO:649) AT GGA GGG CGG CAT GG -3' (Fragment 643) (SEQ. ID NO:650) AT GGA GGG CGG CAT G -3' (Fragment 644) (SEQ. ID NO:651) AT GGA GGG CGG CAT -3' (Fragment 645) (SEQ. ID NO:652) AT GGA GGG CGG CA-3' (Fragment 646) (SEQ. ID NO:653) AT GGA GGG CGG C-3' (Fragment 647) (SEQ. ID NO:654) AT GGA GGG CGG -3' (Fragment 648) (SEQ. ID NO:655) AT GGA GGG CG -3' (Fragment 649) (SEQ. ID NO:656) T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 650) (SEQ. ID NO:657) T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 651) (SEQ. ID NO:658) T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 652) (SEQ. ID NO:659) T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 653) (SEQ. ID NO:660) T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 654) (SEQ. ID NO:661) T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 655) (SEQ. ID NO:662)

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C GGG CAC AGG CTG GGC-3' (Fragment 875) (SEQ. ID NO:882)
5'-
5'-
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       C GGG CAC AGG CTG G-3' (Fragment 877) (SEQ. ID NO:884)
       C GGG CAC AGG CTG -3' (Fragment 878) (SEQ. ID NO:885)
       C GGG CAC AGG CT-3' (Fragment 879) (SEO. ID NO:886)
       C GGG CAC AGG C-3' (Fragment 880) (SEQ. ID NO:887)
5'-
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        AC AGG CTG GGC-3' (Fragment 900) (SEQ. ID NO:907)
        AC AGG CTG GG-3' (Fragment 901) (SEQ. ID NO:908)
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(Fragment 904) (SEQ. ID NO:911)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
(Fragment 905) (SEQ. ID NO:912)
5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
(Fragment 906) (SEQ. ID NO:913)
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(Fragment 907) (SEQ. ID NO:914)
5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 908) (SEQ. ID NO:915) 5'-CTG GAA
AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 909) (SEQ. 1D NO:916)
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5'-GC GGG CAC AGG CTG GGC-3' (Fragment 937) (SEQ. ID NO:944)
5'-C GGG CAC AGG CTG GGC-3' (Fragment 938) (SEQ. ID NO:945)
5'-GGG CAC AGG CTG GGC-3' (Fragment 939) (SEQ. ID NO:946)
5'-GG CAC AGG CTG GGC-3' (Fragment 940) (SEQ. ID NO:947)
5'-G CAC AGG CTG GGC-3' (Fragment 941) (SEQ. ID NO:948)
5'-CAC AGG CTG GGC-3' (Fragment 942) (SEQ. ID NO:949)
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5'-AC AGG CTG GGC-3' (Fragment 943) (SEQ. ID NO:950)
5'-C AGG CTG GGC-3' (Fragment 944) (SEQ. ID NO:951)
5'-AGG CTG GGC-3' (Fragment 945) (SEQ. ID NO: 952)
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Other adenosine fragments, for example those with low adenosine content or lacking adenosine altogether, are also suitable and in some cases even preferred, for use with the invention. The following sequences, their fragments and combinations, are one particularly preferred group of anti-sense oligos.

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TTT TCC TTC CTT TGT CTC TCT TC (FRAG 946) (SEQ. ID NO: 953)
GCT CCC GGC TGC CTG (FRAG 947) (SEQ. ID NO: 954)
CTC GGC CGT GCG GCT CTG TCG CTC CCG GT (FRAG 948) (SEQ. ID NO: 955)
CCG CCG CCC TCC GGG GGG TC (FRAG 949) (SEQ. ID NO: 956)
TGC TGC CGT TGG CTG CCC (FRAG 950) (SEQ. ID NO: 957)
CTT CTG CGG GTC GCC GG (FRAG 951) (SEQ. ID NO: 958)
TGC TGG GCT TGT GGC (FRAG 952) (SEQ. ID NO: 959)
GGC CTC TCT TCT GGG (FRAG 953) (SEQ. ID NO: 960)
CCT GGT CCC TCC GT (FRAG 954) (SEQ. ID NO: 961)
GGT GGC TCC TCT GC (FRAG 955) (SEQ. ID NO: 962)
GCT TGG TCC TGG GGC TGC (FRAG 956) (SEQ. ID NO: 963)
TGC TCT CCT CTC CTT (FRAG 957) (SEQ. ID NO: 964)
```

In another embodiment of this invention, the oligos are anti-sense to an adenosine A_{2a} receptor, and must either "up-regulate" it, or if they have some adenosine A_1 activity they are treated as the other anti-sense oligos. The following sequences are preferred examples of anti-sense oligos associated with the human adenosine A_{2a} receptor. Another preferred group is composed of fragments of these sequences as-generally-described above, and combinations thereof, as well as mixtures. Also preferred are these sequences, fragments and their combinations where one or more adenosines are substituted by a universal base or an adenosine analogue which either is not an agonist or a ligand for the adenosine A_1 receptor, or which acts as an antagonist of the A_1 receptor, such as, for example, theophylline or enprophylline.

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5'-TGC TTT TCT TTT CTG GGC CTC-3' (FRAG 958) (SEQ. ID NO: 965)
5'-TGT GGT CTG TTT TTT TCT G-3' (FRAG 959) (SEQ. ID NO: 966)
5'-GCC CTG CTG GGG CGC TCT CC-3' (FRAG 960) (SEQ. ID NO: 967)
5'-GCC GCC CGC CTG GCT CCC-3' (FRAG 961) (SEQ. ID NO: 968)
5'-GGB GCC CBT GBT GGG CBT GCC-3' (FRAG 962) (SEQ. ID NO: 969)
5'-GTG GTT CTT GCC CTC CTT TGG CTG-3' (FRAG 963) (SEQ. ID NO: 970)
5'-CCG TGC CCG CTC CCC GGC-3' (FRAG 964) (SEQ. ID NO: 971)
5'-CTC CTG GCG GGT GGC CGT TG-3' (FRAG 965) (SEQ. ID NO: 972)
5'-GCC CTG TT CC CTT GGG-3' (FRAG 966) (SEQ. ID NO: 973)
5'-GCC TGG GGC TCC CTT CTC TC-3' (FRAG 967) (SEQ. ID NO: 974)
5'-GCC CTT CTT GCT GGG CCT C-3' (FRAG 968) (SEQ. ID NO: 975)
5'-TGC TGC TGC TGC TGT GGC CCC C-3' (FRAG 969) (SEQ. ID NO: 976)
GTACACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC (FRAG 970) (SEQ. ID NO: 977)
GTBCBCCGBGGGGGCCCBTGBTGGGCBTGCCBCBGBCGBCGGC (FRAG 971) (SEQ. ID NO: 978)
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As indicated above, also included in this patent are all types of adenosine A_{2a} agonists, whether or not they are nucleic acids. These are known in the art and must generally have agonistic A_{2a} activity and either lack or have low adenosine A_1 agonistic activity and/or have antagonistic adenosine A_1 activity.

In another embodiment, the anti-sense oligo of the invention may be a sequence which is antisense to the adenosine A_{2b} receptor. By means of example, the following sequences associated with the human receptor are provided. These sequences as well as their fragments and combinations, desadenosine fragments and those where one or more A are substituted with a universal base or adenosine analogue as described above are preferred. 5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG-3' (FRAG 972) (SEQ. ID NO: 979)
5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 973) (SEQ. ID NO: 980)
5'-TTG GCC CGC GCG CCC CGT CTC GGG CTG GGC GG-3 (FRAG 974) (SEQ. ID NO: 981)
5'-CGG GTC GGG GCC CCC CGC GGC C-3' (FRAG 975) (SEQ. ID NO: 982)
5'-GCC TCG GGG CTG GGG CGC TGG TGG CCG GG-3' (FRAG 976) (SEQ. ID NO: 983)
5'-CCG CGC CTC CGC CTG CCG CTT CTG-3' (FRAG 977) (SEQ. ID NO: 984)
5'-GCT GGG CCC CGG GCG CCC CCT-3' (FRAG 978) (SEQ. ID NO: 985)
5'-CCC CTC TTG CTC GGG TCC CCG TG-3' (FRAG 979) (SEQ. ID NO: 986)
ACAGCGCGTCCTGTGTCTCCAGCAGCATGGCCGGGCCAGCTGGGCCCC (FRAG 980) (SEQ. ID NO: 987)
BCBGCGCGTCCTGTGTCTCCBGCBGCBTGGCCGGGCCBGCTGGGCCCC (FRAG 981) (SEQ. ID NO: 988)

In still another embodiment, the oligo of this invention may be anti-sense to any fragment of the adenosine A₃ receptor gene or mRNA, including overlapping regions with the flanking regions or introns. The following are examples of these fragments associated with the human receptor. These are preferred sequences. Also preferred are their fragments and combinations, as well as desadenosine fragments and those where one or more A are substituted by a universal base or A analogue as described above.

ACA GAG CA TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G (FRAG 982) (SEQ. ID NO: 989) BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT CCC BGG G (FRAG 983) (SEQ. ID NO: 990) CCC TTT TCT GGT GGG GTG (FRAG 984) (SEQ. ID NO: 994) GTG CTG TTG TG GGC (FRAG 985) (SEQ. ID NO: 992) TTT CTT CTG TTC CC (FRAG 986) (SEQ. ID NO: 993) CCC TTT TCT GGT GGG GTG (FRAG 987) (SEQ. ID NO: 994) GTG CTG TTG TTG GGC (FRAG 988) (SEQ. ID NO: 995) TTT CTT CTG TTC CC (FRAG 989) (SEQ. ID NO: 996)

In the anti-sense oligonucleotides of the present invention, exemplified by the preceding sequences, a number of adenosine bases may be replaced with an appropriate "spacer" or universal base (e.g., 1-[\beta-D-2'-deoxyribofuranosyl]-5-nitroindole], or with an adenosine agonist or antagonist that does not stimulate (or inhibit) adenosine A₁, A_{2b} or A₃ receptors but may stimulate the A_{2a} receptor. A preferred universal base for the treatment of SVT is one that exhibits adenosine A2a agonsitic activity. In this manner, a specific adenosine receptor gene may be targeted to obtain one or more anti-sense oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding mRNA, and then, if necessary, their content of adenosine may be reduced by substituting one or more universal bases or adenosine analogues incapable of activating adenosine A₁, A_{2b} or A₃ receptors or which activate the adenosine A_{2a} receptor. Thus, in addition to "down-regulating" specific adenosine receptor genes, the present oligos have an increased effect when administered by either selection of genes, RNA and flanking regions that are devoid, or have a low A content, or alternatively one or more of the adenosine(s) present in the oligonucleotide(s) are substituted with other nucleotide bases, so called universal bases, which bind to thymidine (T) but lack the ability to activate adenosine receptors and otherwise may not activate adenosine receptors. Given that adenosine (A) is a nucleotide base complementary to thymidine (T), when a T appears in the RNA, the anti-sense oligo will have an A at the same position.

The method of the present invention may be used to treat ailments associated with or causing cardiac, lung and/or renal damage, and even failure in a subject, regardless of its cause. The anti-sense agent(s) of the invention have preferably a low (or reduced) A content to prevent its liberation upon in vivo degradation of the agent(s), preferably up to about 15%, more preferably up to about 10%, still

more preferably up to about 5%, and even more preferred being devoid of A ("desadenosine oligos").

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%. This method may also comprise, when the selected fragment comprises at least one thymidine base, substituting an adenosine base in the corresponding nucleotide of the anti-sense fragment with a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A1, A2b and A3 receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A2a receptor. The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, NH2, SH, SO, SO2, SO3, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkynyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH2, primary, secondary and tertiary amine, SH, SO, SO2, SO3, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimidines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein R¹ and R² are independently H, alkyl, alkenyl or alkynyl and R³ is H, aryl, dicycloalkyl, dicycloalkynyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkyl, O-cycloalkynyl, O-cycloalkynyl, NH₂-alkylamino-ketoxyalkyloxy-aryl, mono and dialkylaminoalkyl-N-alkylamino-SO₂aryl, among others. However, other methods may also be employed. The inventor reduced the adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target gene, RNA, flanking regions, and bridging sections to less than about 15%, or fully eliminated A from the oligonucleotide sequence as a means for preventing their breakdown products from freeing adenosine into the lung tissue environment and, thereby, aggravating the subject's ailment and/or countering the beneficial effect of the administered agent.

Also part of this invention are chemical analogues of oligonucleotides in which, for example, the phosphodiester bonds have been modified, e.g., to a methylphosphonate, a phosphotriester, a

phosphorothioate, a phosphorodithioate, or a phosphoramidate, or that other portions of the molecule have been modified, so as to render the oligonucleotide more stable in vivo. The naturally occurring phosphodiester linkages in oligonucleotides are susceptible to degradation by endogenously occurring cellular nucleases, while many analogous linkages are highly resistant to nuclease degradation. See Milligan et al., and Cohen, J. S., supra. The use of a "3'-end cap" strategy by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3'-end of the oligonucleotide protects oligonucleotides from degradation. See, Tidd, D. M. and Warenius, H.M., Br. J. Cancer 60, 343-350 (1989); Shaw, J.P. et al., Nucleic Acids Res. 19, 747-750 (1991). Phosphoramidate, phosphorothioate, and methylphosphonate linkages are suitable for use in this invention. In addition, extensive modification of the phosphodiester backbone has been shown to impart stability and may allow for enhanced affinity and increased cellular permeation of oligonucleotides. See Milligan, et al., supra. Many different chemical strategies have been employed to replace the entire phosphodiester backbone with novel linkages. Id. The analogues of the oligonucleotides of the invention include phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, boranophosphate, phosphotriester, formacetal, 2'-0-methyl, 3'-thioformacetal, 5'-thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfonamide, sulfone, sulfone, sulfide, sulfone, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI) linkages, among others. The oligonucleotides of the invention may also be modified by addition of a terminal 1,3-propanediol or a terminal dodecanol, among others, or they may be conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone, dehydroepiandrosterone sulfate, dehydroepiandrosterone sulfatide, ubiquinone, dolichol, poly L-lysine, sulfatidic acid and fatty acid, among others. The oligos of the invention may also be modified by 2'-O-methoxyethy, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) and peptide nucleic acid interbase linkages. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred because of their availability and suitability for automated oligonucleotide synthesis. Id. Antisense oligonucleotides containing modifications to the nucleotide base itself (e.g., a C-5 propyne) or to the sugar (e.g., a carbohydrate modification), are also aspects of the present invention.

Where appropriate, the antisense nucleotide may be administered in the form of their pharmaceutically acceptable salts or as a mixture. Anti-sense oligonucleotides may be of any suitable length, e.g., from about 7 to 60 nucleotide in length, depending on the particular target being bound and their mode of delivery. Preferably the antisense oligonucleotide is directed to a gene or mRNA region containing a junction between intron and exon. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit the splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g., with the 3' or 5' terminus of the antisense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon. When practicing the present invention, the antisense oligonucleotides administered may be related in origin to the species to which it is administered. When treating humans, the anti-sense may be derived from human sequences. However, sequences

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obtained from one species are also suitable for administration to a second species.

The pharmaceutical compositions provided herein comprise the anti-sense oligos given above. Optionally, the pharmaceutical compositions may also comprise one or more surfactants. Suitable surfactants or surfactant components for enhancing the uptake of the anti-sense oligonucleotides of the invention include synthetic and natural as well as full and truncated forms of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, di-saturated phosphatidylcholine (other than dipalmitoyl), dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine; phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyl-lysophosphatidylcholine, dolichols, dehydroepiandrosterone, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate; as well as natural and artificial lamelar bodies which are the natural carrier vehicles for the components of surfactant, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitinic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric and polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone, among others. These surfactants may be used either as single or part of a multiple component surfactant in-a-formulation, or as covalently bound additions to the 5' and/or 3' ends of the anti-sense oligonucleotides (oligos). These compositions are administered in amounts effective to reduce the expression of an adenosine receptor, such as the adenosine A₁, A_{2b} or A₃ receptor by passing through a cell membrane and binding specifically with mRNA encoding an adenosine A_1 , A_{2b} or A_3 receptor in the cell and prevent its translation. In addition, the present oligos and other agents in general may be targeted to the adenosine A_{2a} receptor to activate this receptor or increase the amount present (agonist activity). Such compositions may contain a suitable pharmaceutically acceptable carrier e.g., sterile pyrogen-free saline solution, and the like. The anti-sense oligonucleotides may be formulated as topical and systemic formulations, in a variety of types, including oral, buccal, nasal, otical, rectal, inhalable, slow release, enteric coated, dermal, intradermal, injectable, and many more as is known in the art. The formulation of the invention may also comprise a hydrophobic carrier capable of passing through a cell membrane, e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier. The oligonucleotides may also be coupled to a substance which inactivates mRNA, such as a ribozyme. The present oligonucleotides may be administered to a subject afficted with any disease or condition associated with the lung adenosine receptors to inhibit the activation of A₁ or A₃ adenosine receptors. The pharmaceutical formulation may also contain chimeric molecules comprising antisense oligonucleotides attached to molecules which are known to be internalized by cells. These oligonucleotide conjugates utilize cellular uptake pathways to increase the cellular concentrations of Examples of macromolecules used in this manner include transferrin, oligonucleotides. asialoglycoprotein (bound to oligonucleotides via polylysine or other chemical linkages) and streptavidin.

In the pharmaceutical formulation the anti-sense compound may be contained within a lipid

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particle or vesicle, such as a liposome or microcrystal. The lipid particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the antisense oligonucleotide is contained therein. Positively charged lipids such as N- [1-(2, 3 -dioleoyloxi) propyl] -N, N, N-trimethyl-ammoniumethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g., U.S. Patent Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

The composition of the invention may be administered by any means which transports the antisense nucleotide composition to the lung. The antisense compounds disclosed herein may be administered to the lungs of a patient by any suitable means, but are preferably administered by inhalation of an aerosol comprised of respirable particles which comprise the anti-sense compound. The respirable particles may be liquid or solid, and they may optionally contain other therapeutic or diagnostic ingredients as well as other typical ingredients for a particular formulation. Examples of other agents are analgesics such as acetominophen, anilerdine, aspirin, buprenorphine, butabital, butorpphanol, Choline Salicylate, Codeine, Dezocine, Diclofenac, Diflunisal, Dihydrocodeine, Elcatoninin, Etodolac, Fenoprofen, Hydrocodone, Hydromorphone, Ibuprofen, Ketoprofen, Ketorolac, Levorphanol, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Meperidine, Methadone, Methotrimeprazine, Morphine, Nalbuphine, Naproxen, Opium, Oxycodone, Oxymorphone, Pentazocine, Phenobarbital, Propoxyphene, Salsalate, Sodium Salicylate, Tramadol and Narcotic analgesics in addition to those listed above. See, Mosby's Physician's GenRx. Anti- anxiety agents are also useful including Alprazolam, Bromazepam, Buspirone, Chlordiazepoxide, Chlormezanone, Clorazepate, Diazepam, Halazepam, Hydroxyzine, Ketaszolam, Lorazepam, Meprobamate, Oxazepam and Prazepam, among others. Anti-anxiety agents associated with mental depression, such as Chlordiazepoxide, Amitriptyline, Loxapine Maprotiline and Perphenazine, among others. Anti-inflammatory agents such as non-rheumatic Aspirin, Choline Salicylate, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Floctafenine, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Salsalate, Sodium Salicylate, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolmetin, anti-inflammatories for ocular treatment such as Diclofenac, Flurbiprofen, Indomethacin, Ketorolac, Rimexolone (generally for post-operative treatment), anti-inflammatories for, non-infectious nasal applications such as Beclomethaxone, Budesonide, Dexamethasone, Flunisolide, Triamcinolone, and the like. Soporifics (anti-insomnia/sleep inducing agents) such as those utilized for treatment of insomnia, including Alprazolam, Bromazepam, Diazepam, Diphenhydramine, Doxylamine, Estazolam, Flurazepam, Halazepam, Ketazolam, Lorazepam, Nitrazepam, Prazepam Quazepam, Temazepam, Triazolam, Zolpidem and Sopiclone, among others. Sedatives including Diphenhydramine, Hydroxyzine, Methotrimeprazine, Promethazine, Propofol, Melatonin, Trimeprazine, and the like. Sedatives and agents used for treatment of petit mal and tremors, among other conditions, such as Amitriptyline HCl; Chlordiazepoxide, Amobarbital; Secobarbital, Aprobarbital, Butabarbital, Ethchiorvynol, Glutethimide, L-Tryptophan, Mephobarbital, MethoHexital Na, Midazolam Hcl, Oxazepam, Pentobarbital Na, Phenobarbital, Secobarbital Na, Thiamylal Na, and many others. Agents used in the treatment of head trauma (Brain Injury/Ischemia), such as Enadoline HCl (e.g. for treatment of severe head injury; orphan status, Warner Lambert), cytoprotective agents, and agents for the treatment of menopause, menopausal symptoms (treatment), e.g. Ergotamine, Belladonna Alkaloids and Phenobarbital, for the treatment of menopausal vasomotor symptoms, e.g. Clonidine, Conjugated Estrogens and Medroxyprogesterone, Estradiol, Estradiol Cypionate, Estradiol Valerate, Estrogens, conjugated Estrogens, esterified Estrone, Estropipate, and Ethinyl Estradiol. Examples of agents for treatment of pre menstrual syndrome (PMS) are Progesterone, Progestin, Gonadotrophic Releasing Hormone, Oral contraceptives, Danazol, Luprolide Acetate, Vitamin B6. Examples of agents for treatment of emotional/psychiatric treatments such as Tricyclic Antidepressants, including Amitriptyline HCl (Elavil), Amitriptyline HCl, Perphenazine (Triavil) and Doxepin HCl (Sinequan). Examples of tranquilizers, anti-depressants and anti-anxiety agents are Diazepam (Valium), Lorazepam (Ativan), Alprazolam (Xanax), SSRI's (selective Ssrotonin reuptake inhibitors), Fluoxetine HCl (Prozac), Sertaline HCl (Zoloft), Paroxetine HCl (Paxil), Fluvoxamine Maleate (Luvox), Venlafaxine HCl (Effexor), Serotonin, Serotonin Agonists (Fenfluramine), and other over the counter (OTC) medications. Also suitable are heart medicines, renal agents, and the like, which are known in the art.

The anti-sense compound may be administered in an anti-cardiac, anti-cardiopulmonary and/or anti-renal damage or failure effective amount which depends upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from about 0.05 to about 50 µM, or more particularly about 0.2 to about 5 µM, are desirable. For administration to a subject such as a human, a dosage of about 0.01, 0.1, or 1 mg/Kg up to about 50, 100, or 150 mg/Kg or more is typically employed. However, other doses are also contemplated in this patent, particularly when varying the route of administration. Depending on the solubility of the active compound in any particular formulation, the daily dose may be divided among one or several unit dose administrations. The administration of the anti-sense compound may be carried out therapeutically, i.e., as a rescue treatment, or prophylactically, alone or in conjunction with other therapeutic or diagnostic agents as described above.

The anti-sense compound of the present invention is preferably administered into the respiratory system, e.g. by inhalation, nasal spraying, or generally into the lungs, as a formulation including particles of respirable size, e.g. particles of a size sufficiently small to pass through the nose, mouth and larynx upon inhalation and through the bronchi and alveoli of the lungs. In general, respirable particles range from about 0.5 to 10 microns in size. Particles of non-respirable size which are included in, for example, an aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is thus minimized. For nasal administration, a particle size in the range of about 10-500 μ m is preferred to ensure retention in the nasal cavity. Other sizes, however, are also suitable as are other routes of administration.

Liquid pharmaceutical compositions of active compound for producing an aerosol may be prepared by combining the antisense compound with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds may optionally be included.

Solid particulate compositions containing respirable dry particles of micronized antisense compound may be prepared by grinding dry antisense compound with a mortar and pestle, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising of the antisense compound may optionally

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contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which may be blended with the antisense compound in any suitable ratio, e.g., a 1 to 1 ratio by weight.

The aerosols of liquid particles comprising the antisense compound may be produced by any suitable means, such as with a nebulizer. See, e.g., U.S. Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

The aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 µl, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereon. In these examples, μM means micromolar, mL means milliliters, μm

means micrometers, mm means millimeters, cm means centimeters, $^{\circ}$ C means degrees Celsius, μg means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h means hours.

EXAMPLES

Example 1: Design and Synthesis of Anti-sense Oligonucleotides & Controls

The design of anti-sense oligonucleotides against the adenosine receptors is based on the primary and secondary structure of the target receptor mRNA. The anti-sense oligonucleotide are selected, and optimally modified, to target regions of mRNA which confer functional activity or stability to the mRNA and which preferably may overlap the initiation codon. For instance, regions that afford particularly strong binding, such as CG strings are preferred, i.e. runs of G and/or C preferably at the 5'-end of the target region within the target gene or mRNA. However, other target sites within the molecule are suitable as well, particularly those which have low sequence overlapping with other gene sequences, thus increasing the specificity of the treatment.

Other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis (controls), are included as controls in anti-sense experiments to demonstrate the specificity of the activity of the agents of this invention.

The primary and secondary structure of the human adenosine A₁ receptor mRNA was analyzed and used as described above to design anti-sense oligonucleotides, including the ones, whose sequences are provided. One anti-sense oligonucleotide (Oligo I) was synthesized as a phosphorothioate, designated HAdAlAS, and has the following sequence:

5'-GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)

As a control, a mis-matched phosphorothioate anti-sense nucleotide designated HAdAlMM was synthesized with the following sequence.

5' -GTA GCA GGC GGG GAT GGG GGC-3' (SEQ ID NO:2)

The oligonucleotides of SEQ. ID NOS: 1 and 2 shown above have identical base contents and general sequence structures. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A₁ receptor genes, and that the mis-matched control was not a candidate for hybridization with any known gene sequence.

In the same manner, the primary and secondary structure of the human adenosine A₃ receptor mRNA was analyzed and various oligos selected, and the following two synthesized as phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized has the following sequence.

5'-GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3)

As a control, a mis-matched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, which has the following sequence.

5' -GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:4)

The second phosphorothicate anti-sense oligonucleotide (HadA3AS2) has the following sequence.

5' -GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5)

As a control, its mis-matched oligonucleotide (HAdA3MM2) has the following sequence.

5' -GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:6)

All phosphorothioate oligonucleotides were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

Example 2: In Vitro Testing of A₁-Adenosine Receptor Anti-sense Oligonucleotides

The anti-sense oligonucleotide against the human A_1 receptor (SEQ ID NO:1) described above was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the A_1 adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

HTB-54 human lung adenocarcinoma cells (106/100 mm tissue culture dish) were exposed to 5.0 μM HAdAlAS or HAdAlMM for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdAlAS-treated, HAdAlMM-treated and non-treated HTB-54 cells. These blots showed clearly that HAdAlAS but not HAdAlMM effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdAlAS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A₁ receptor, which is involved in asthma.

Example 3: In Vivo Efficacy of A₁ Adenosine Receptor Anti-sense Oligonucleotides

A fortuitous homology between the rabbit and human DNA sequences within the adenosine A_1 gene overlapping the initiation codon permitted the use of the phosphorothioate anti-sense oligonucleotides initially designed for use against the human adenosine A_1 receptor in a rabbit model.

Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/mL house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly.

The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer

(Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (Cdyn) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT).

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Animals were randomized and on Day 1 pretreatment values for PC50 were obtained for aerosolized adenosine. Anti-sense (HAdAlAS) or mismatched control (HAdAlMM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000 µg (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000 µg in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, PA), producing aerosol droplets 80% of which were smaller than 5 µm in diameter.

In the first arm of the experiment, four randomly selected allergic rabbits were administered antisense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide.

Following a 1 week interval, animals were crossed over, with those previously administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC50 values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in both Figure 1 and Table 1.

<u>Table 1</u>: Adenosine A₁ Receptor Anti-sense Oligonucleotide Effect upon PC50 Values in Asthmatic Rabbits

Mismatch Control		A ₁ Receptor Anti-sense Oligonucleotide		
Pre oligonucleotide	Post oligonucleotide	Pre oligonucleotide	Post oligonucleotide	
3.56 ± 1.02	5.16 ± 1.93	2.36 ± 0.68	>19.5 ± 0.34**	

Results are presented as the mean (n=8)*SEM. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected t test. **Significantly different from all other groups, P < 0.01.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC50 values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide.

These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that down regulation of the adenosine A₁ receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyperresponsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an important human disease.

Example 4: Specificity of A₁-adenosine Receptor Anti-sense Oligonucleotide

At the conclusion of the crossover experiment of Example 3, airway smooth muscle from all rabbits was quantitatively analyzed for adenosine A_1 receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine A_2 receptors, which should not have been affected, were also quantified.

Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to described methods (Kleinstein, J., and Glossmann, H., Naunyn-Schmiedeberg's Arch. Pharmacol. 305, 191-200 (1978), with slight modifications. Crude plasma membrane preparations were stored at -70°C until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976)). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. The binding of [³H] DPCPX (A₁ receptor-specific) or [³H] CGS-21680 (A₂ receptor-specific) was measured as previously described. See, Ali, S., et al., J. Pharmacol. Exp. Ther. 268, 1328-1334 (1994); S. Ali et al., Am. J. Physiol. 266, L271-277 (1994).

As illustrated in both Figure 2 and Table 2, animals treated with adenosine A_1 anti-sense oligonucleotide in the crossover experiment had a nearly 75% decrease in A_1 receptor number compared to controls, as assayed by specific binding of the A_1 -specific antagonist DPCPX. There was no change in adenosine A_2 receptor number, as assayed by specific binding of the A_2 receptor-specific agonist 2- [p-(2-carboxyethyl)-phenethylamino] -5'-(N-ethylcarboxamido) adenosine (CGS-21680).

<u>Table 2</u>: Specificity or Action of Adenosine A Receptor Anti-sense Oligonucleotide

	Mismatch Control Oligonucleotide	A ₁ -Anti-sense Oligonucleotide
	(Mean ± SD) n=8	(Mean <u>+</u> SD) n=8
A ₁ -Specific Binding	1,105 ± 48**	293 ± 18
A ₂ -Specific Binding	. 302 ± 22**	442 ± 171

Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected t test. **Significantly different from mismatch control, p < 0.01.

Example 5: In Vivo Response to Adenosine Challenge with & without Oligo I Pretreatment

Two hyper responsive monkeys (ascaris sensitive) were challenged with inhaled adenosine, with and without pre-treatment with anti-sense oligo I (SEQ.ID NO: 1). The PC₄₀ adenosine was calculated from the data collected as being equivalent to that amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways.

The Oligo I (SEQ. ID NO:1; EPI 2010) was subsequently administered at 10 mg/day for 2 days by inhalation. On the third day, PC adenosine was again measured. The results are shown in Figure 3 accompanying this patent. The left bar shows the PC40 adenosine value prior to treatment with Oligo I whereas the right bar shows the PC40 adenosine taken after administration of Oligo I. As can be seen in Figure 3, any sensitivity to adenosine was completely eliminated by the administration of the oligo of this invention in one animal, and substantially reduced in the second.

Example 6: Anti-sense Oligos directed to other Target Nucleic Acids

This work was conducted to demonstrate that the present invention is broadly applicable to antisense oligonucleotides ("oligos") specific to nucleic acid targets broadly. The following experimental studies were conducted to show that the method of the invention is broadly suitable for use with antisense oligos designed as taught by this application and targeted to any and all adenosine receptor mRNAs. For this purpose, various anti-sense oligos were prepared to adenosine receptor mRNAs exemplified by the adenosine A_1 , A_{2b} and A_3 receptor mRNAs.

Anti-sense Oligo I was disclosed above (SEQ. ID NO: 1). Five additional anti-sense phosphorothioate oligos were designed asnd synthesized as indicated above.

- 1- Oligo II (SEQ. ID NO: 997) also targeted to the adenosine A_1 receptor, but to a different region than Oligo I.
 - 2- Oligo V (SEQ. ID NO: 1000) targeted to the adenosine A_{2b} receptor.
- 3- Oligos III (SEQ. ID NO: 998) and IV (SEQ. ID NO: 999) targeted to different regions of the adenosine A_3 receptor.
 - 4- Oligo I-PD (SEQ. ID NO:1)(a phosphodiester oligo of the same sequence as Oligo I).

These anti-sense oligos were designed for therapy on a selected species as described above and are generally specific for that species, unless the segment of the target mRNA of other species happens

to contain a similar sequences. All anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

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Example 7: Design & Sequences of other Anti-sense Oligos

Six oligos and their effects in Sa rabbit model were studied and the results of these studies are reported and discussed below. Five of these oligos were selected for this study to complement the data on Oligo I (SEQ ID NO: 1) provided in Examples 1 to 4 above. This oligo is anti-sense to one region of the adenosine A₁ receptor mRNA.

The oligos tested are identified as anti-sense Oligos I (SEQ ID NO: 1) and II (SEQ. ID No: 997) targeted to a different region of the adenosine A₁ receptor mRNA, Oligo V (SEQ. ID No: 998) targeted to the adenosine A_{2b} receptor mRNA, and anti-sense Oligos III and IV (SEQ. ID NOS: 999 and 1000) targeted to two different regions of the adenosine A₃ receptor mRNA. The sixth oligo (Oligo I-PD) is a phosphodiester version of Oligo I (SEQ. ID NO: 1). The design and synthesis of these anti-sense oligos was performed in accordance with Example 1 above.

(I) Anti-sense Oligo I

The anti-sense oligonucleotide I referred to in Examples 1 to 5 above is targeted to the human A_1 adenosine receptor mRNA (EPI 2010). Anti-sense oligo I is 21 nucleotide long, overlaps the initiation codon, and has the following sequence.

5'- GAT GGA GGG CGG CAT GGC GGG -3' (SEQ. ID No:1)

The oligo I was previously shown to abrogate the adenosine-induced bronchoconstriction in allergic rabbits, and to reduce allergen-induced airway obstruction and bronchial hyperresponsiveness (BHR), as discussed above and shown by Nyce, J. W. & Metzger, W. J., Nature, 385:721 (1977), the relevant portions of which reference are incorporated in their entireties herein by reference.

(II) Anti-sense Oligo II

A phosphorothioate anti-sense oligo (SEQ. ID NO:997) was designed in accordance with the invention to target the rabbit adenosine A_1 receptor mRNA region +936 to +956 relative to the initiation codon (start site). The anti-sense oligo II is 21 nucleotide long, and has the following sequence.

5'-CTC GTC GCC GTC GCC GGC GGG-3' (SEQ. ID NO:997)

(III) Anti-sense Oligo III

A phosphorothioate anti-sense oligo other than that provided in Example 1 above (SEQ. ID NO:998) was designed in accordance with the invention to target the anti-sense A_3 receptor mRNA region +3 to + 22 relative to the initiation codon start site. The anti-sense oligo III is 20 nucleotide long, and has the following sequence.

5'-GGG TGG TGC TAT TGT CGG GC-3' (SEQ. ID NO:998)

(IV) Anti-sense Oligo IV

Yet another phosphorothioate anti-sense oligo (SEQ. ID NO:999) was designed in accordance with the invention to target the adenosine A_3 receptor mRNA region + 386 to + 401 relative to the initiation codon (start site). The anti-sense oligo IV is 15 nucleotide long, and has the following

sequence.

5'-GGC CCA GGG CCA GCC-3' (SEQ. ID NO:999)

(V) Anti-sense Oligo V

A phosphorothioate anti-sense oligo (SEQ. ID NO:1000) was designed in accordance with the invention to target the adenosine A_{2b} receptor mRNA region -21 to -1 relative to the initiation codon (start site). The anti-sense oligonucleotide V is 21 nucleotide long, and has the following sequence.

5'-GGC CGG GCC AGC CGG GCC CGG-3' (SEQ. ID NO:1000)

(VI) A₁ Mismatch Oligos

Two different mismatched oligonucleotides having the following sequences were used as controls for anti-sense oligo I (SEQ. ID NO: 1) described in Example 6 above.

A₁ MM2 5'-GTA GGT GGC GGG CAA GGC GGG-3' (SEQ. ID NO:1002)

A₁ MM3 5'-GAT GGA GGC GGG CAT GGC GGG-3' (SEQ. ID NO:1003)

Anti-sense oligo I and the two mismatch anti-sense oligos had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligo I was specific, not only for the human, but also for the rabbit, adenosine A₁ receptor genes, and that the mismatched controls were not candidates for hybridization with any known human or animal gene sequence.

(VII) Anti-sense Oligo A₁-PD (Oligo VI)

A phosphodiester anti-sense oligo (Oligo VI; SEQ. ID NO:1004) having the same nucleotide sequence as Oligo I was designed as disclosed in the above-identified application. Anti-sense oligo I-PD is 21 nucleotide long, overlaps the initiation codon, and has the following sequence.

5'- GAT GGA GGG CGG CAT GGC GGG -3' (SEQ. ID NO:1004)

VIII) Controls

Each rabbit was administered 5.0 ml aerosolized sterile saline following the same schedule as for the anti-sense oligos in (II), (III), and (IV) above.

Example 8: Synthesis of Anti-sense Oligos

Phosphorothioate anti-sense oligos having the sequences described in (a) above, were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis. Anti-sense oligonucleotide II (SEQ. ID NO: 997), anti-sense oligonucleotide III (SEQ. ID NO: 998) and anti-sense oligonucleotide IV (SEQ. ID NO: 999) were each synthesized and purified in this manner.

Example 9: Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp. 347-362, CRC Press, Boca Raton (1990); Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149: 908 (1994)), the

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relevant portions of which are incorporated in their entireties here by reference. Immunizations were repeated weekly for the first month and then biweekly until the age of 4 months. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149 (1994)), the relevant section being incorporated in its entirety here by reference.

DOSE-RESPONSE STUDIES

Example 10: Experimental Setup

Aerosols of either adenosine (0-20 mg/ml), or anti-sense or one of two mismatch oligonucleotides (5 mg/ml) were separately prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5µm in diameter. Equal volumes of the aerosols were administered directly to the lungs *via* an intratracheal tube.

The animals were randomized, and administered aerosolized adenosine. Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC₅₀ Adenosine). The animals were then administered either the aerosolized anti-sense or one of the mismatch anti-sense oligos via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC₅₀ values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in Example 21 below.

Example 11: Crossover Experiments

For some experiments utilizing anti-sense oligo I (SEQ. ID NO:1) and a corresponding mismatch control oligonucleotide A1MM2, following a 2 week interval, the animals were crossed over, with those previously administered the mismatch control A_1MM2 , now receiving the anti-sense oligo I, and those previously treated with the anti-sense oligo I, now receiving the mismatch control A_1MM2 oligo.

The number of animals per group was as follows. For mismatch A₁MM2 (Control 1), n=7, since one animal was lost in the second control arm of the experiment due to technical difficulties, for mismatch A₁MM3 n=4 (Control 2) and for A₁AS anti-sense oligo I, n=8. The A₁MM3 oligo-treated animals were analyzed separately and were not part of the cross-over experiment. The treatment methods and measurements employed following the cross-over were identical to those employed in the first arm of the experiment.

In 6 of the 8 animals treated with the anti-sense oligo I (SEQ. ID NO:1), no PC₅₀ value could be obtained for adenosine doses of up to 20 mg/ml, which is the limit of solubility of adenosine. Accordingly, the PC₅₀ values for these animals were assumed to be 20 mg/ml for calculation purposes. The values given, therefore, represent a minimum figure for the effectiveness of the anti-sense

oligonucleotides of the invention. Other groups of allergic rabbits (n=4 for each group) were administered 0.5 or 0.05 mg doses of the anti-sense oligo I (SEQ ID NO:1), or the A₁MM2 oligo in the manner and according to the schedule described above (the total doses being 2.0 or 0.2 mg). The results of these studies are provided in Example 23 below.

Example 12: Anti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I (SEQ. ID NO:1) in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

The results obtained for anti-sense oligo I and its mismatch controls confirmed that the mismatch controls are equivalent to saline, as described in Example 20 below and in Table 1 of Nyce & Metzger, Nature 385, 721-725 (1997). Because of this finding, saline was used as a control for pulmonary function studies employing anti-sense oligos II, III and IV (SEQ. ID NOS: 997, 998 and 999).

Example 13: Specificity of Oligo I for Adenosine A, Receptor (Receptor Binding Studies)

Tissue from airway smooth muscle was dissected to primary, secondary and tertiary bronchi from rabbits which had been administered 20 mg oligo I (SEQ. ID NO:1) in 4 divided doses over a period of 48 hours as described above. A membrane fraction was prepared according to the method of Ali et al. (Ali, S., et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994), the relevant section relating to the preparation of the membrane fraction is incorporated in its entirety hereby by reference).

The protein content was determined by the method of Bradford and plasma membranes were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. See, Bradford, M. M. Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference. The binding of [³H]DPCPX, [³H]NPC17731, or [³H]CGS-21680 was measured as described by Jarvis et al. See, Jarvis, M.F., et al., Pharmacol. Exptl. Ther. 251, 888-893 (1989), the relevant portion of which is fully incorporated herein by reference. The results of this study are shown in Table 8 and discussed in Example 21below.

Example 14: Pulmonary Function Measurements (Compliance cpyn and Resistance)

At 4 months of age, the immunized animals were anesthetized and relaxed with 1.5 ml of a mixture of ketamine HCl (35 mg/kg) and acepromazine maleate (1.5 mg/kg) administered intramuscularly. After induction of anesthesia, allergic rabbits were comfortably positioned supine on a soft molded animal board. Salve was applied to the eyes to prevent drying, and they were closed. The animals were then intubated with a 4.0 mm intermediate high-low cuffed Murphy 1 endotracheal tube (Mallinckrodt, Glen Falls, NY), as previously described by Zavala and Rhodes. See, Zavala and Rhodes, Proc. Soc. Exp. Biol. Med. 144: 509-512 (1973), the relevant portion of which is incorporated herein by reference in its entirety. A polyethylene catheter of OD 2.4 mm (Becton Dickinson, Clay Adams, Parsippany NJ) with an attached thin-walled latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiment. The endotracheal

tube was attached to a heated Fleisch pneumotach (size 00; DEM Medical, Richmond, VA), and the flow (v) measured using a Validyne differential pressure transducer (Model DP-45-16-1927, Validyne Engineering, Northridge, CA), driven by a Gould carrier amplifier (Model 11-4113, Gould Electronics, Cleveland, OH).

An esophageal balloon was attached to one side of the Validyne differential pressure transducer, and the other side was attached to the outflow of the endotracheal tube to obtain transpulmonary pressure (P_{tp}). The flow was integrated to yield a continuous tidal volume, and the measurements of total lung resistance (R_t) and dynamic compliance (C_{dyn}) were made at isovolumetric and zero flow points. The flow, volume and pressure were recorded on an eight channel Gould 2000 W high-frequency recorder and C_{dyn} was calculated using the total volume and the difference in P_{tp} at zero flow, and . R_t was calculated as the ratio of P_{tp} and V at midtidal lung volumes. These calculations were made automatically with the Buxco automated pulmonary mechanics respiratory analyzer (Model 6, Buxco Electronics, Sharon, C_{tp}), as previously described by Giles et al. See, Giles et al., Arch. Int. Pharmacodyn. Ther. 194: 213-232 (1971), the relevant portion of which describing these calculations is incorporated in toto hereby by reference. The results obtained upon administration of oligo II on allergic rabbits are shown and discussed in Example 27below.

Example 15: Measurement of Bronchial Hyperresponsiveness (BHR)

Each allergic rabbit was administered histamine by aerosol to determine their baseline hyperresponsiveness. Aerosols of either saline or histamine were generated using a DeVilbiss nebulizer (DeVilbiss, Somerset, PA) for 30 seconds and then for 2 minutes at each dose employed. The ultrasonic nebulizer produced aerosol droplets of which 80% were <5 micron in diameter. The histamine aerosol was administered in increasing concentrations (0.156 to 80 mg/ml) and measurements of pulmonary function were made after each dose. The B4R was then determined by calculating the concentration of histamine (mg/ml) required to reduce the C_{dyn} 50% from baseline (PC₅₀ Histamine).

Example 16: Cardiovascular Effect of Anti-sense Oligo I

The measurement of cardiac output and other cardiovascular parameters using CardiomaxTM utilizes the principal of thermal dilution in which the change in temperature of the blood exiting the heart after a venous injection of a known volume of cool saline is monitored. A single rapid injection of cool saline was made into the right atrium via cannulation of the right jugular vein, and the corresponding changes in temperature of the mixed injectate and blood in the aortic arch were recorded via cannulation of the carotid artery by a temperature-sensing miniprobe.

Twelve hours after the allergic rabbits had been treated with aerosols of oligo I (EPI 2010; SEQ. ID NO: 1) as described in (d) above, the animals were anesthetized with 0.3 ml/kg of 80% Ketamine and 20% Xylazine. This time point coincides with previous data showing efficacy for SEQ. ID NO: 1, as is clearly shown by Nyce & Metzger, (1997), supra, the pertinent disclosure being incorporated in its entirety here by reference. A thermocouple was then inserted into the left carotid artery of each rabbit, and was then advanced 6.5 cm and secured with a silk ligature. The right jugular vein was then cannulated and a length of polyethylene tubing was inserted and secured.

A thermodilution curve was then established on a CardiomaxTM II (Columbus Instruments, Ohio) by injecting sterile saline at 20°C to determine the correctness of positioning of the thermocouple probe. After establishing the correctness of the position of the thermocouple, the femoral artery and vein were isolated. The femoral vein was used as a portal for drug injections, and the femoral artery for blood pressure and heart rate measurements. Once constant baseline cardiovascular parameters were established, CardiomaxTM measurements of blood pressure, heart rate, cardiac output, total peripheral resistance, and cardiac contractility were made.

Example 17: Duration of Action of Oligo I (SEQ. ID NO: 1)

Eight allergic rabbits received initially increasing log doses of adenosine by means of a nebulizer via an intra-tracheal tube as described in (f) above, beginning with 0.156 mg/ml until compliance was reduced by 50% (PC50 Adenosine) to establish a baseline. Six of the rabbits then received four 5 mg aerosolized doses of (SEQ. ID NO:1) as described above. Two rabbits received equivalent amounts of saline vehicle as controls. Beginning 18 hours after the last treatment, the PC50 Adenosine values were tested again. After this point, the measurements were continued for all animals each day, for up to 10 days. The results of this study are discussed in Example 26 below.

Example 18: Reduction of Adenosine A_{2b} Receptor Number by Anti-sense Oligo V

Sprague Dawley rats were administered 2.0 mg respirable anti-sense oligo V (SEQ. ID NO:1000) three times over two days using an inhalation chamber as described above. Twelve hours after the last administration, lung parenchymal tissue was dissected and assayed for adenosine A_{2b} receptor binding using [311]-NECA as described by Nyce & Metzger (1997), supra. Controls were conducted by administration of equal volumes of saline. The results are significant at p<0.05 using Student's paired t test, and are discussed in Example 29 below.

Example 19: Comparison of Oligo I & Corresponding Phosphodiester Oligo VI (SEQ. ID NO:1004)

Oligo I (SEQ ID NO:1) countered the effects of adenosine and eliminated sensitivity to it for adenosine amounte up to 20 mg adenosine/5.0 ml (the limit of solubility of adenosine). Oligo VI (SEQ. ID NO:1004), the phosphodiester version of the oligonucleotide sequence, was completely ineffective when tested in the same manner. Both compounds have identical sequence, differing only in the presence of phosphorothioate residues in Oligo I (SEQ ID NO:1), and were delivered as an aerosol as described above and in Nyce & Metzger (1997), supra. Significantly different at p<0.001, Student's paired t test. The results are discussed in Example 30 below.

RESULTS OBTAINED FOR ANTI-SENSE OLIGO I (SEQ. ID NO: 1)

Example 20: Results of Prior Work

The nucleotide sequence and other data for anti-sense oligo I (SEQ. ID NO:1), which is specific for the adenosine A₁ receptor, were provided above. The experimental data showing the effectiveness of

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oligo I in down regulating the receptor number and activity were also provided above.

Further information on the characteristics and activities of anti-sense oligo I is provided in Nyce, J. W. and Metzger, W. J., Nature 385:721 (1997), the relevant parts of which relating to the following results are incorporated in their entireties herein by reference. The Nyce & Metzger (1997) publication provided data showing that the anti-sense oligo I (SEQ. ID NO:1):

- (1) The anti-sense oligo I reduces the number of adenosine A_1 receptors in the bronchial smooth muscle of allergic rabbits in a dose-dependent manner as may be seen in Table 3 below.
- (2) Anti-sense Oligo I attenuates adenosine-induced bronchoconstriction and allergen-induced bronchoconstriction.
- (3) The Oligo I attenuates bronchial hyperresponsiveness as measured by PC₅₀ histamine, a standard measurement to assess bronchial hyperresponsiveness. This result clearly demonstrates anti-inflammatory activity of the anti-sense oligo I as is shown in Table 2 above.
- (4) As expected, because it was designed to target it, the anti-sense oligo I is totally specific for the adenosine A_1 receptor, and has no effect at all at any dose on either the very closely related adenosine A_2 receptor or the related bradykinin B_2 receptor. This is seen in Table 3 below.
- (5) In contradistinction to the above effects of the Oligo I, the mismatch control molecules MM2 and MM3 (SEQ. ID NO:1002 and SEQ. ID NO:1003) which have identical base composition and molecular weight but differed from the anti-sense oligo I (SEQ ID NO: 1) by 6 and 2 mismatches, respectively. These mismatches, which are the minimum possible while still retaining identical base composition, produced absolutely no effect upon any of the targeted receptors (A₁, A₂ or B₂).

These results, along with a complete lack of prior art on the use of anti-sense oligonucleotides, such as oligo I, targeted to the adenosine A_1 receptor, are unexpected results. The showings presented in this patent clearly enable and demonstrate the effectiveness, for their intended use, of the claimed agents and method for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, allergy(ies), and the like.

Example 21: Oligo I Significantly Reduces Response to Adenosine Challenge

The receptor binding experiment is described in Example 13 above, and the results shown in Table 3 below which shows the binding characteristics of the adenosine A₁-selective ligand [₃H]DPCPX and the bradykinin B₂-selective ligand [³H]NPC 17731 in membranes isolated from airway smooth muscle of A₁ adenosine receptor and B₂ bradykinin receptor anti-sense- and mismatch-treated allergic rabbits.

Table 3: Binding Characteristics of Three Anti-Sense Oligos

Treatment ¹	A, receptor		B ₂ receptor	
	Kd	$\mathbf{B}_{\mathbf{max}}$	Kd	Bmax
Adenosine A ₁	Receptor			
20 mg	0.36±0.029 nM	19±1.52 fmoles*	0.39±0.031 nM	14.8±0.99fmoles
2 mg	$0.38 \pm 0.030 \text{ nM}$	32±2.56 fmoles*	$0.41 \pm 0.028 \text{ nM}$	15.5±1.08 fmoles
0.2 mg	0.37 ± 0.030 nM	49±3.43 fmoles	0.34±0.024 nM	15.0±1.06 fmoles
A ₁ MM1	(Control)			
20 mg	$0.34 \pm 0.027 \text{ nM}$	52.0±3.64 fmoles	0.35±0.024 nM	14.0±1.0 fmoles
2 mg	0.37±0.033 nM	51.8±3.88 fmoles	0.38±0.028 nM	14.6±1.02 fmoles
B ₂ A (Bradykinin	Receptor)			
20 mg	$0.36\pm0.028~\text{nM}$	45.0±3.15 fmoles	0.38±0.027 nM	8.7±0.62 fmoles*
2 mg	$0.39 \pm 0.035 \text{ nM}$	44.3±2.90 fmoles	0.34±0.024 nM	11.9±0.76 fmoles**
0.2 mg	0.40±0.028 nM	47.0±3.76 fmoles	0.35±0.028 nM	15.1±1.05 fmoles
B ₂ MM (Control)				
20 mg	0.39±0.031 nM	42.0±2.94 fmoles	0.41±0.029 nM	14.0±0.98 fmoles
2 mg	0.41±0.035 nM	40.0±3.20 fmoles	0.37±0.030 nM	14.8±0.99 fmoles
0.2 mg	$0.37 \pm 0.029 \text{ nM}$	43.0±3.14 fmoles	0.36±0.025 nM	15.1±1.35 fmoles
Saline Control	0.37±0.041	46.0±5.21	0.39±0.047 nM	14.2±1.35 fmoles

Refers to total oligo administered in four equivalently divided doses over a 48 hour period. Treatments and analyses were performed as described in methods. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey=s protected t test. N = 4-6 for all groups.

Example 21: Dose-response Effect of Oligo I

Anti-sense oligo I (SEQ ID NO:1) was found to reduce the effect of adenosine administration to the animal in a dose-dependent manner over the dose range tested as shown in Table 4 below.

<u>Table 4</u>: Dose-Response Effect to Anti-sense Oligo I

Total Dose (mg)	PC50 Adenosine (mg Adenosine)
Anti-sense Oligo I	
0.2	8.32 ± 7.2
2.0	14.0 ± 7.2
20	19.5±0.34
A ₁ MM2 oligo (control)	
0.2	2.51 ± 0.46
2.0 20	3.13 ± 0.71 3.25 ± 0.34
20	3.25 ± 0.34

The above results were studied with the Student=s paired t test and found to bestatistically different, p=0.05

Significantly different from mismatch control- and saline-treated groups, p<0.001;
 Significantly different from mismatch control- and saline-treated groups, p<0.05.

The oligo I (SEQ. ID NO:1), an anti-adenosine A_1 receptor oligo, acts specifically on the adenosine A_1 receptor, but not on the adenosine A_2 receptors. These results stem from the treatment of rabbits with anti-sense oligo I (SEQ. ID NO:1) or mismatch control oligo (SEQ. ID NO:1002; A_1 MM2) as described in Example 9 above and in Nyce & Metzger (1997), supra (four doses of 5 mg spaced 8 to 12 hours apart via nebulizer via endotracheal tube), bronchial smooth muscle tissue excised and the number of adenosine A_1 and adenosine A_2 receptors determined as reported in Nyce & Metzger (1997), supra.

Example 23: Specificity of Oligo I (SEQ. ID NO:1) for Target Gene Product

Oligo I (SEQ. ID No:1) is specific for the adenosine A₁ receptor whereas its mismatch controls had no activity. Figure 1 depicts the results obtained from the cross-over experiment described in Example 10 above and in Nyce & Metzger (1997), supra. The two mismatch controls (SEQ. ID NO:1002 and SEQ. ID NO:1003) evidenced no effect on the PC₅₀ Adenosine value. On the contrary, the administration of anti-sense oligo I (SEQ. ID NO:1) showed a seven-fold increase in the PC₅₀ Adenosine value. The results clearly indicate that the anti-sense oligo I (SEQ. ID NO:1) reduces the response (attenuates the sensitivity) to exogenously administered adenosine when compared with a saline control. The results provided in Table 2 above clearly establish that the effect of the anti-sense oligo I is dose dependent (see, column 3 of Table 1).

The Oligo I was also shown to be totally specific for the adenosine A_1 receptor, (see, top 3 rows of Table), inducing no activity at either the closely related adenosine A_2 receptor or the bradykinin B_2 receptor (see, lines 8-10 of Table 2 above).

In addition, the results shown in Table 2 establish that the anti-sense oligo I (SEQ. ID NO:1) decreases sensitivity to adenosine in a dose dependent manner, and that it does this in an anti-sense oligo-dependent manner since neither of two mismatch control oligonucleotides (A₁MM2; SEQ. ID NO:1002 and A₁MM3; SEQ. ID NO:1003) show any effect on PC_{50 Adenosine} values or on attenuating the number of adenosine A₁ receptors.

Example 24: Effect on Aeroallergen-induced Bronchoconstriction & Inflammation

The Oligo I (SEQ. ID NO:1) was shown to significantly reduce the histamine-induced effect in the rabbit model when compared to the mismatch oligos. The effect of the anti-sense Oligo I (SEQ. ID No:1) and the mismatch oligos (A₁MM2, SEQ. ID NO:1002 and A₁MM3, SEQ. ID NO:1003) on allergen-induced airway obstruction and bronchial hyperresponsiveness was assessed in allergic rabbits.

The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced airway obstruction was assessed. As calculated from the area under the plotted curve, the anti-sense oligo I significantly inhibited allergen-induced airway obstruction when compared with the mismatched control (55%, p<0.05; repeated measures ANOVA, and Tukey's t test).

A complete lack of effect was induced by the mismatch oligo A₁MM2 (Control) on allergen induced airway obstruction.

The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced BHR was determined as above. As calculated from the PC_{50 Histamine} value, the anti-sense oligo I (SEQ. ID NO:1) significantly inhibited allergen-induced BHR in allergic rabbits when compared to the mismatched control (61%, p<0.05; repeated measures ANOVA, Tukey's t test).

A complete lack of effect of the A₁MM mismatch control on allergen-induced BHR was observed.

The results indicated that anti-sense oligo I (SEQ. ID NO: 1) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ. ID NO:1) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti- inflammatory activity for anti-sense oligo I (SEQ. ID NO:1).

Example 25: Anti-sense Oligo I is Free of Deleterious Side Effects

The Oligo I (SEQ. ID NO:1) was shown to be free of side effects that might be toxic to the recipient. No changes in arterial blood pressure, cardiac output, stroke volume, heart rate, total peripheral resistance or heart contractility (dPdT) were observed following administration of 2.0 or 20 mg oligo I (SEQ. ID NO:1). The addition, the results of the measurement of cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), and contractility (dPdT) with a Cardiomax™ apparatus (Columbus Instruments, Ohio) were assessed.

These results evidenced that oligo I (SEQ. ID NO:1) has no detrimental effect upon critical cardiovascular parameters. More particularly, this oligo does not cause hypotension. This finding is of particular importance because other phosphorothioate anti-sense oligonucleotides have been shown in the past to induce hypotension in some model systems. Furthermore, the adenosine A₁ receptor plays an important role in sinoatrial conduction within the heart. Attenuation of the adenosine A₁ receptor by anti-sense oligo I (SEQ. ID NO:1) might be expected to result, therefore, in deleterious extrapulmonary activity in response to the downregulation of the receptor. This is not the case. The anti-sense oligo I (SEQ. ID NO:1) does not produce any deleterious intrapulmonary effects and renders the administration of the low doses of the present anti-sense oligo free of unexpected, undesirable side effects.

This demonstrates that when oligo I (SEQ. ID NO:1) is administered directly to the lung, it does not reach the heart in significant quantities to cause deleterious effects. This is in contrast to traditional adenosine receptor antagonists like theophylline which do escape the lung and can cause deleterious, even life-threatening effects outside the lung.

Example 26: Long Lasting Effect of Oligo I

The Oligo I (SEQ. ID NO:1) evidenced a long lasting effect as evidenced by the PC₅₀ and Resistance values obtained upon its administration prior to adenosine challenge.

The duration of the effect was measured for with respect to the PC₅₀ of adenosine anti-sense oligo I when administered in four equal doses of 5 mg each by means of a nebulizer via an endotracheal tube, as described above. The effect of the agent is significant over days 1 to 8 after administration.

When the effect of the anti-sense oligo I (SEQ. ID NO:1) had disappeared, the animals were administered saline aerosols (controls), and the PC₅₀ Adenosine values for all animals were measured again. Saline-treated animals showed base line PC₅₀ adenosine values (n=6).

The duration of the effect (with respect to Resistance) was measured for six allergic rabbits which were administered 20 mg of anti-sense oligo I (SEQ. ID NO: 1) as described above, upon airway resistance measured as also described above. The mean calculated duration of effect was 8.3 days for both PC50 adenosine (p<0.05) and resistance (p<0.05). These results show that anti-sense oligo I (SEQ. ID NO:1) has an extremely long duration of action, which is completely unexpected.

Example 27: Anti-sense Oligo III -

Anti-sense oligo II, targeted to a different region of the adenosine A_1 receptor mRNA, was found to be highly active against the adenosine A_1 -mediated effects. The experiment measured the effect of the administration of anti-sense oligo II (SEQ. ID NO:997) upon compliance and resistance values when 20 mg anti-sense oligo II or saline (control) were administered to two groups of allergic rabbits as described above. Compliance and resistance values were measured following an administration of adenosine or saline as described above in Example 13. The effect of the anti-sense oligo of the invention was different from the control in a statistically significant manner, p<0.05 using paired t-test, compliance; p<0.01 for resistance.

The results showed that anti-sense oligo II (SEQ. ID NO:997), which targets the adenosine A_1 receptor, effectively maintains compliance and reduces resistance upon adenosine challenge.

Example 28: Antisense Oligos III and IV

Oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) were shown to be in fact specifically targeted to the adenosine A₃ receptor by their effect on reducing inflammation and the number of inflammatory cells present upon separate administration of 20 mg of the anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) to allergic rabbits as described above. The number of inflammatory cells was determined in their bronchial lavage fluid 3 hours later by counting at least 100 viable cells per lavage.

The effect of anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) upon granulocytes, and upon total cells in bronchial lavage were assessed following exposure to dust mite allergen. The results showed that the anti-sense oligo IV (SEQ. ID NO:999) and anti-sense oligo III (SEQ. ID NO:998) are very potent anti-inflammatory agents in the asthmatic lung following exposure to dust mite allergen. As is known in the art, granulocytes, especially eosinophils, are the primary inflammatory cells of asthma, and the administration of anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) reduced their numbers by 40% and 66%, respectively. Furthermore, anti-sense oligos IV (SEQ. ID NO:999) and III (SEQ. ID NO:998) also reduced the total number of cells in the bronchial lavage fluid by 40% and 80%, respectively. This is also an important indicator of anti-inflammatory activity by the present anti-adenosine A₃ agents of the invention. Inflammation is known to underlie bronchial hyperresponsiveness and allergen-induced bronchoconstriction in asthma. Both anti-sense oligonucleotides III (SEQ. ID NO:998) and IV (SEQ. ID NO:999), which are targeted to the adenosine

A₃ receptor, are representative of an important new class of anti-inflammatory agents which may be designed to specifically target the lung receptors of each species.

Example 29: Anti-sense Oligo V

The anti-sense oligo V (SEQ. ID NO:1000) , targeted to the adenosine A_{2b} adenosine receptor mRNA was shown to be highly effective at countering adenosine A_{2b} -mediated effects and at reducing the number of adenosine A_{2b} receptors present to less than half.

Example 30: Unexpected Superiority of Substituted over Phosphodiester-residue Oligo I-DS (SEQ. ID NO:1681)

Oligos I (SEQ. ID NO:1) and I-DS (SEQ. ID NO:1) were separately administered to allergic rabbits as described above, and the rabbits were then challenged with adenosine. The phosphodiester oligo I-DS (SEQ. ID NO:1) was statistically significantly less effective in countering the effect of adenosine whereas oligo I (SEQ. ID NO:1) showed high effectiveness, evidencing a PC50 Adenosine of 20 mg.

Example 31: Anti-sense Oligo VI

For the present work, I designed an additional anti-sense phosphorothioate oligo targeted to the adenosine A₁ receptor (Oligo VI). This anti-sense oligo was designed for therapy on a selected species as described in the above patent application and is generally specific for that species, unless the segment of the adenosine receptor mRNA of other species elected happens to have a similar sequence. The anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and lung allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

One additional oligo and its effect in a rabbit model was studied and the results of the study are reported and discussed below. The present oligo (anti-sense oligo VI) was selected for this study to complement the data on SEQ ID NO: 1 (Oligo I), which is anti-sense to the adenosine A₁ receptor mRNA provided in the above-identified patent application. This additional oligo is identified as anti-sense Oligo VI, and is targeted to a different region of the adenosine A₁ receptor mRNA than Oligo I. The design and synthesis of this anti-sense oligo was performed in accordance with the teaching, particularly Example 1, of the above-identified patent application.

The anti-sense Oligo VI is a phosphorothioate designed to target the coding region of the rabbit adenosine A_1 receptor mRNA region +964 to +984 relative to the initiation codon (start site). The Oligo VI was prepared as described in the above-indicated application, and is 20 nucleotides long. The OligoVI is directed to the adenosine A_1 receptor gene, and has the following sequence.

5'-CGC CGG CGG GTG CGG GCC GG-3' (SEQ. ID NO:1004)

The phosphorothioate anti-sense Oligo VI having the sequence described in (5) above, was synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the

sulfurizing agent during the synthesis.

Example 32: Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp 347-362, CRC Press, Boca Raton, 1990; Ali, S. Et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994)).

The immunizations were repeated weekly for the first month and then bi-weekly until the animals were 4 months old. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (1994), supra.

Example 33: Adenosine Aerosol Preparation

An adenosine aerosol (20 mg/ml) was prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5µm in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube to all three rabbits.

The animals were then administered the aerosolized adenosine and Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC₅₀ Adenosine). The animals were then administered the aerosolized anti-sense via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC₅₀ values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in (9) below.

Example 34: Anti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

Example 35: Oligo VI Reduces Response to Adenosine Challenge as Well or Better than Oligo I

Oligo VI was tested in three allergic rabbits of the characteristics and readied as described in (7) above and in the above-indicated patent application. Oligo VI targets a section of the coding region of the A_1 receptor which is different from Oligo I. Both these target sequences were selected randomly from many possible coding region target sequences.

The three rabbits were treated identically as previously indicated for Oligo I. Briefly, 5 mg of

Oligo VI were nebulized to the rabbits twice per day at 8 hour intervals, for two days. Thereafter, PC₅₀ adenosine studies were performed on the morning of the third day and compared to pre-treatment PC₅₀ values. This protocol is described in more detail in Nyce and Metzger (Nyce & Metzger, Nature 385: 721-725 (1997)). The results obtained for the three rabbits are shown in Table 5 below.

<u>Table 5</u>: PC₅₀ Adenosine before & after Aerosolized Adenosine Treatment

Treatment Time	PC ₅₀ Adenosine (mg)	
Pre-treatment	3.0 ±2.1	
Post-treatment	>20.0*	

^{*} maximum achievable dose due to adenosine insolubility in saline

All three animals treated with Oligo VI completely eliminated sensitivity to adenosine up to the measurable level of the agent shown in Table 1 above. That is, the administration of the Oligo VI abrogated the adenosine-induced bronchoconstriction in the three allergic rabbits. The actual efficacy of Oligo VI is, therefore, greater than could be measured in the experimental system used.

By comparing with the previously submitted results for the Oligo I, it may be seen that the Oligo VI was found to be as effective, or more, than Oligo I.

Example 36: Determination of Surfactant Depletion When A1 Receptors Are Expressed in Lung

This example shows the effect on the oligos of the invention on the level of lung phospholipid in an animal model for hypersensitivity to the adenosine A_1 receptor. The leftmost column of Figure 4 shows the level of phospholipid present in the untreated allergic rabbit. When the adenosine A_1 receptors in allergic rabbits were stimulated by aerosolized adenosine, there was a significant depletion of lung surfactant. See middle column in Figure 4. The administration of an an anti-sense oligonucleotide which has been shown to block adenosine A_1 receptor expression (SEQ. ID NO:1). See, Nyce, JW and Metzger, WJ, Nature (1997). When oligo I (SEQ. ID NO:1) was administered to the allergic rabbit prior to the administration of adenosine, this adenosine A_1 receptor-induced surfactant depletion was completely prevented. See rightmost column in Figure 4. This indicates that attenuation of the adenosine A_1 receptor by administration of the present anti-sense oligonucleotides establishes normal surfactant secretion. This is applicable to the prevention of RDS by administration during gestation of the composition of the invention comprising either a down-regulating oligo for the A_1 receptor or any agonist capable of stimulating the A_{2a} receptor. This would be very beneficial because currently available surfactant preparations used in the treatment of RDS are either incomplete or derived from animal sources.

Example 37:

Rabbits were administered 5 mg oligo I (SEQ. ID NO:1; EPI 2010) or saline (control) by

nebulizer twice a day for two days and were then challenged with bacterial endotoxin administered by ear vein injection. Neutrophils, a key inflammatory cell in ARDS, were then quantitated ($\eta = 3$). The leftmost column represents a saline control (saline administered to the rabbit - same volume as treatment). The center column represents the high number of neutrophils elicited by treatment with endotoxin alone. The rightmost column shows a significant (statistically) decrease in the number of neutrophils produced upon treatment with the oligo I. The data are shown in Figure 5. The results of the experimental test show a clear reduction in the number of neutrophils in the bronchial lavage fluid obtained from the oligo I treated animals.

Example 38:

As in example 37, rabbits were administered 5 mg oligo I (SEQ. ID NO:1; EPI 2010) or saline (control) by nebulizer twice a day for two days and were then challenged with bacterial endotoxin administered by ear vein injection. The left-hand column represents the edema produced by bacterial endotoxin, and the right-hand column shows the prevention or alleviation of edema brought about by the oligo of the invention. Thus, the data show that oligo I (EPI 2010) reduced the lung edema caused by bacterial endotoxin.

Example 39:

Rabbits were administered 5 mg oligo I (SEQ. ID NO:1; EPI 2010) or saline (control) by nebulizer twice a day for two days, and were then challenged with bacterial endotoxin administered by ear vein injection. The total number of cells, an indication of inflammation, was then quantitated in bronchial lavage fluid obtained from each animal ($\eta = 3$). The results show a dramatic increase in the total number of cells upon challenge with bacterial endotoxin (middle bar) when compared to saline (leftmost bar). Finally, the administration of 5 mg of oligo I shows a pronounced reduction in the total number of cells elicited by the endotoxin.

Example 40: Conclusions

The work described and results discussed in the examples clearly show that all anti-sense oligonucleotides designed in accordance with the teachings of this patent were found to be highly effective at countering or reducing effects mediated by the receptors they are targeted to. That is, each and all of the two anti-sense oligos targeting an adenosine A_1 receptor mRNA, 1 anti-sense oligo targeting an adenosine A_{2b} receptor mRNA, and the 2 anti-sense oligos targeting an A_3 receptor mRNA were shown capable of countering the effect of exogenously administered adenosine which is mediated by the specific receptor they are targeted to.

The activity of the anti-sense oligos of this invention, moreover, is specific to the target and substitutively fails to inhibit another target. In addition, the results presented also show that the administration of the present agents results in extremely low or non-existent deleterious side effects or toxicity.

This represents 100% success in providing agents that are highly effective and specific in the treatment of bronchoconstriction and/or inflammation. This invention is broadly applicable in the same

manner to all gene(s) and corresponding mRNAs encoding proteins involved in or associated with airway diseases.

A comparison of the phosphodiester and a version of the same oligonucleotide wherein the phosphodiester bonds are substituted with phosphorothioate bonds evidenced an unexpected superiority for the phosphothiorate oligonucleotide over the phosphodiester anti-sense oligo.

The foregoing examples are illustrative of the present invention, but are not to be construed as limiting thereof. The invention is furter defined by the following claims, with equivalents of the claims to be included therein.

Claims

1. A pharmaceutical composition, comprising

an agent which, when administered to a subject is effective for preventing, alleviating and/or inhibiting adenosine-mediated cardiopulmonary and/or renal damage and/or failure, the agent being selected from the group consisting of

adenosine A2a receptor agonist agents,

nucleic acids which comprise one or more oligonucleotide (oligo) selected from the group consisting of oligos that are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A1, A2a, A2b and A3 receptors having agonist activity at the an adenosine A1, A2b or A3 receptors or lacking agonist or having antagonist activity at the adenosine A2a receptor, which contain about 0 to less than about 15% adenosine (A), and

mixtures thereof; and

optionally one or more surfactants.

- 2. The composition of claim 1, wherein the oligo consists of up to about 10% A.
- 3. The composition of claim 2, wherein the oligo consists of up to about 5% A.
- 4. The composition of claim 3, wherein the oligo is A-free.
- 5. The composition of claim 4, further comprising an agent selected from the group consisting of diagnostic and therapeutic agents, preferably selected from the group consisting of adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating (agonist) agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, anti-allergic rhinitis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS and ARDS), pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, liver, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, imaging agents, cardiac stress testing agents, antibody therapy agents, phototherapeutic agents, adenosine, and other anti-arrhythmic agents.
- 6. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and flanking regions thereof of the adenosine A₁ receptor, which have agonistic activity, and of the adenosine A2a receptor which have antagonistic or lack adenosine A2a receptor activity, and optionally one or more surfactants.
- 7. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and flanking regions thereof of the adenosine A_{2b} and A₃ receptors having adenosine A_{2b} and A₃ receptor agonistic activity, and optionally one or more surfactants.

- 8. The composition of claim 1, wherein one or more adenosines (A) is(are) substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to thymidine base but have antagonist or agonist activity of less than about 0.5 of the adenosine base agonist or antagonist activity at the adenosine A_1 , A_{2a} , A_{2b} and A_3 receptors.
- 9. The composition of claim 1, wherein the agent is an adenosine A2a agonist agent, and the composition optionally comprises one or more surfactants.
- 10. The composition of claim 8, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH₂, SH, SO, SO₂, SO₃, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH₂, primary, secondary and tertiary amine, SH, SO, SO₂, SO₃, cycloalkyl, heterocycloalkyl and heteroaryl.
- 11. The composition of claim 10, wherein the pyrimidines and purines are substituted at positions selected from the group consisting of positions 1, 2, 3, 4, 7 and 8.
- 12. The composition of claim 11, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein R^1 and R^2 are independently H, alkyl, alkenyl or alkynyl and R^3 is H, aryl, dicycloalkyl, dicycloalkynyl, cycloalkyl, cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, NH₂-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO₂ aryl.

- 13. The composition of claim 12, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.
- 14. The composition of claim 1, where one methylated cytosine (mC) is substituted for an unmethylated cytosine (C) if at least one CpG dinucleotide if present in the oligo(s).
- 15. The composition of claim 1, wherein at least one mononucleotide residue of the antisense oligonucleotide(s) is a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methylmino), (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy (methylimino) (MOMA), methoxy methyl (MOM), 2'-O-methyl, phosphoramidate, and C-5 substituted residues, and combinations thereof.

- 16. The composition of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to about 60 mononucleotides.
- 17. The composition of claim 1, wherein the anti-sense oligonucleotide is selected from the group consisting of SEQ ID NOS.: 1, 3, 5, 7 and fragments 1-957 (SEQ. ID NO: 8-952) of SEQ. ID NO: 7 and SEQ. ID NOS: 953-999.
- 18. The composition of claim 1, wherein the anti-sense oligonucleotide is linked to an agent selected from the group consisting of cell internalized or up-taken agent(s) and cell targeting agents, which agent is preferably selected from the group consisting of transferrin, asialoglycoprotein and streptavidin.
 - 19. The composition of claim 18, wherein the nucleic acid is linked to a vector.
 - 20. A vector, comprising the oligo of claim 19, wherein the vector is selected from the group consisting of prokaryotic or eukaryotic vectors.
 - 21. A cell, comprising the oligo of claim 1.
- 22. The composition of claim 1, further comprising a carrier, preferably a biologically acceptable carrier, and more preferably a pharmaceutically or veterinarily acceptable carrier.
- 23. The composition of claim 22, wherein the carrier is selected from the group consisting of gaseous, liquid, solid carriers and mixtures thereof.
- 24. The composition of claim 23, further comprising an agent selected from the group consisting of diagnostic and other therapeutic agents, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, surfactants, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives.
- 25. The composition of claim 24, comprising the agent, a therapeutic agent, a surfactant and a pharmaceutically acceptable carrier.
- The composition of claim 24, wherein the diagnostic and therapeutic agents are selected from the group consisting of other adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating agents, anti-inflammatory agents, contrast imaging agents, cardiac stress testing agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), ARDS, RDS, allergic rhinitis, hypoxia, cardiopulmonary and renal damage or failure, and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents and phototherapeutic agents.
- 27. The composition of claim 24, wherein the RNA inactivating agent comprises an enzyme, preferably a ribozyme.
- 28. The composition of claim 1, wherein the agent is present in an amount of about 0.01 to about 99.99 w/w of the composition, preferably about 1 to about 40 w/w of the composition.
- 29. A formulation, comprising the composition of claim 24, selected from the group consisting of systemic and topical formulations, preferably selected from the group consisting of oral, intrabuccal, intrapulmonary, rectal, intraturerine, intratumor, intracranial, nasal, intramuscular,

subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable, iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release and enteric coating formulations.

- 30. The formulation of claim 29, which is an oral formulation, wherein the carrier is selected from the group consisting of solid and liquid carriers.
- 31. The formulation of claim 30, wherein the liquid carrier is selected from the group consisting of solutions, suspensions, and oil-in-water and water-in-oil emulsions.
- 32. The formulation of claim 30, which is selected from the group consisting of a powder, dragees, tablets, capsules, sprays, aerosols, solutions, suspensions and emulsions.
- 33. The formulation of claim 29, which is a topical formulation, wherein the carrier is selected from the group consisting of creams, gels, ointments, sprays, aerosols, patches, solutions, suspensions and emulsions.
- 34. The formulation of claim 29, which is an injectable formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
 - 35. The formulation of claim 29, which is a rectal formulation in the form of a suppository.
- 36. The formulation of claim 29, which is a transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
- 37. The formulation of claim 36, which is an iontophoretic transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions, and wherein the formulation further comprises a transdermal transport promoting agent.
 - 38. An implantable capsule or cartridge, comprising the formulation of claim 36.
- 39. The formulation of claim 29, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
- 40. The formulation of claim 29, wherein the carrier comprises a hydrophobic carrier, which is preferably lipid vesicles or particles, more preferably comprising liposomes or microcrystals.
- 41. The formulation of claim 40, wherein the vesicles comprise liposomes which comprise the agent.
- 42. The formulation of claim 40, wherein the vesicles comprise N-(1-[2, 3-dioleoxyloxi] propyl) -N,N,N- trimethyl- ammonium methylsulfate.
- 43. The formulation of claim 29, comprising a respirable or inhalable formulation, preferably an aerosol.
 - 44. The formulation of claim 29, in single or multiple unit form, or in bulk.
- 45. A kit for preventing or treating cardiac, lung and/or renal damage or failure, ARDS, RDS, comprising

a delivery device;

in a separate container, the formulation of claim 29; and

instructions for its use; and optionally, in a separate container, an agent selected from the group

consisting of other therapeutic and diagnostic agents, surfactants, solvents, anti-oxidants, flavoring, fillers, volatile oils, dispersants, antioxidants, flavoring agents, propellants, preservatives and buffering, RNA inactivating, cell-internalized or up-taken and coloring agents.

- 46. The kit of claim 45, wherein the delivery device comprises a nebulizer which delivers single metered doses of the formulation.
 - 47. The kit of claim 46, wherein

the nebulizer comprises an insufflator; and

the composition is provided in a piercable or openable capsule or cartridge.

48. The kit of claim 45, wherein

the delivery device comprises a pressurized inhaler; and

the composition comprises a suspension, solution or dry formulation of the agent and/or a solvent.

- 49. The kit of claim 45, comprising, in separate containers, a nucleic and therapeutic agents selected from the group consisting of other anti adenosine A₁, A_{2b} and A₃ receptor antagonists, adenosine A_{2a} receptor stimulants (agonists), anti-inflammatory agents, anti-bacterials, heart, lung and kidney activity maintenance and restoration agents, anti-cancer agents, adenosine, blood pressure controlling agents, and diuretics.
- 50. The kit of claim 45, wherein the solvent is selected from the group consisting of organic solvents and organic solvents mixed with one or more co-solvents.
 - 51. The kit of claim 45, wherein the composition is provided in a capsule or cartridge.
- 52. An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to a subject suspected of being at risk for or being afflicted with, cardiac, lung and/or renal damage or failure, acute respiratory distress syndrome (ARDS), RDS, the composition of claim 1, comprising an amount of the agent effective for preventing or treating cardiac, lung and/or renal damage or failure, ARDS, RDS, anti-ARDS amount of the nucleic acid effective to reach and act on the target polynucleotide.
- 53. A method of preventing, alleviating or countering for preventing or treating adenosine receptor mediated cardiac, lung and/or renal damage or failure, acute respiratory distress syndrome (ARDS), RDS, allergic rhinitis and COPD, comprising conducting the method of claim 52.
- 54. The method of claim 52, wherein the composition is administered into the subject's respiratory system.
 - 55. The method of claim 52, wherein the agent is an adenosine A2a agonist agent, the amount of agent administered is an anti-ARDS or anti-RDS associated bronchoconstriction effective amount, and the method is for preventing or treating ARDS.
 - 56. The method of claim 52, wherein the agent is an adenosine A1 antagonist agent, the amount of agent administered is an anti-COPD associated bronchoconstriction effective amount, and the method is for preventing or treating COPD.
 - 57. The method of claim 52, wherein the agent is an oligo anti-sense to the adenosine A3 receptor mRNA, the amount of agent administered is an anti-allergic rhinitis effective effective amount, and the method is for preventing or treating allergic rhinitis.
 - 58. The method of claim 52, wherein the amount of agent administered is an anti-pulmonary,

- cardiac or renal hypoxic effective amount, and the method is for preventing or treating lung, heart and/or kidney damage and/or failure.
- 59. The method of claim 52, wherein the amount of agent administered is effective for preventing or treating cardiopulmonary hypoxia associated with the administration of stress test agents.
- 60. The method of claim 52, wherein the amount of agent administered effective for preventing or treating renal damage and/or failure associated with the administration od imaging agents.
- 61. The method of claim 52, wherein the agent is effective to reduce the production or availability or to increase the degradation of adenosine receptor mRNA or to reduce the amount of the adenosine receptor.
- 62. The method of claim 52, wherein the agent is administered directly into the subject's lung (s).
- 63. The method of claim 52, wherein the agent is administered as a respirable aerosol.
 - 64. The method of claim 52, wherein the disease or condition is associated with acute inflammation.
- 65. The method of claim 52, wherein the diagnostic or therapeutic agent is selected from the group consisting of adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, (RDS), acute respiratory distress syndrome (ARDS), allergic rhinitis, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents, phototherapeutic agents, adenosine, and other anti-arrhythmic agents.
- 66. The method of claim 52, wherein the therapeutic agent is selected from the group consisting of anti-adenosine A₃ receptor agents.
 - 67. The method of claim 55, wherein ARDS is associated with sepsis.
- 68. The method of claim 52, wherein the composition is administered by a transdermal or systemic route.
- 69. The method of claim 68, wherein the composition is administered orally, intracavitarily, intranasally, intraanally, intravaginally, intrauterally, intraarticularly, transdermally, intrabucally, intravenously, subcutaneously, intradurally, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranially, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, intrathecally, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a pump.
 - 70. The method of claim 52, wherein the subject is a mammal.
- 71. The method of claim 70, wherein the mammals are selected from the group consisting of humans and animals.

- 72. The method of claim 71, wherein the mammal is a human.
- 73. The method of claim 71, wherein the subject is an animal.
- 74. The method of claim 52, wherein the anti-sense oligonucleotide is administered in amount of about 0.005 to about 150 mg/kg body weight.
- 75. The method of claim 74, wherein the anti-sense oligonucleotide is administered in an amount of about 0.01 to about 75 mg/kg body weight.
- 76. The method of claim 75, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to 50 mg/kg body weight.
 - 77. The method of claim 52, which is a prophylactic or preventative method.
 - 78. The method of claim 52, which is a therapeutic method.
 - 79. The method of claim 52, wherein the oligo is obtained by
- (a) selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C;
- (b) obtaining a first oligonucleotide 4 to 60 nucleotide long which comprises the selected fragment and has a C and G nucleic acid content of about 0 to and including about 15%; and
- (c) obtaining a second oligonucleotide 4 to 60 nucleotide long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an A base content of up to and including about 15%.

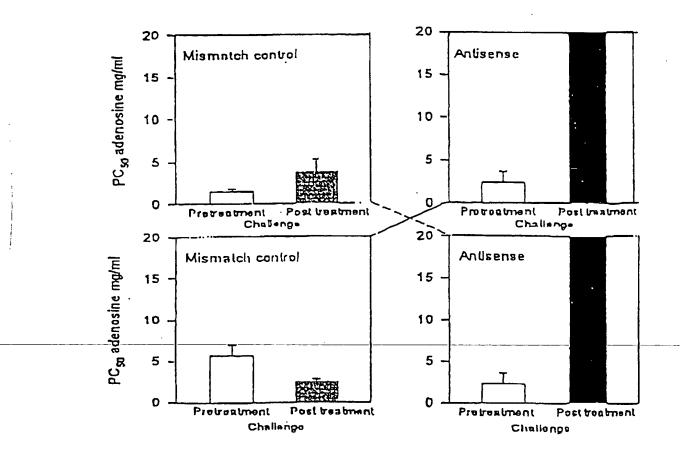
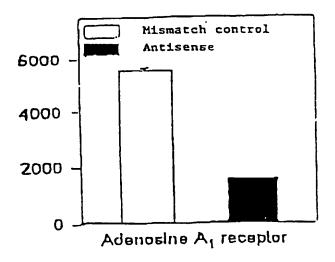


FIGURE 1



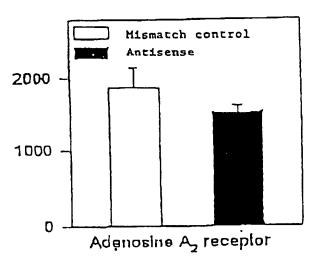


FIGURE 2

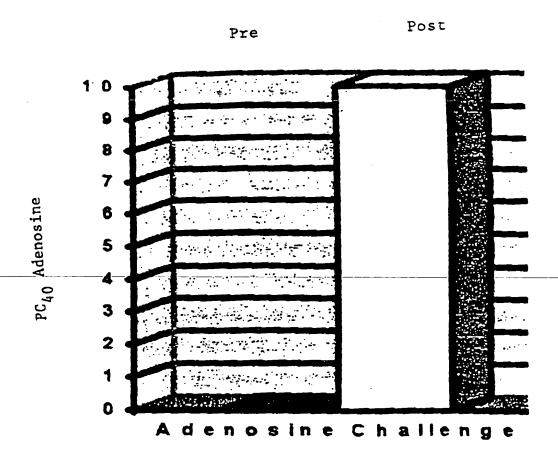


FIGURE 3A Monkey 1

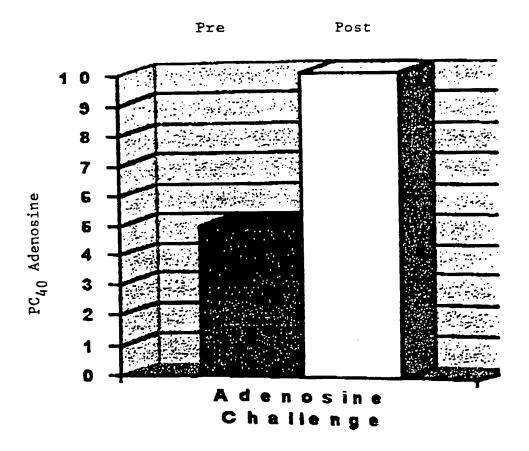


FIGURE 3B

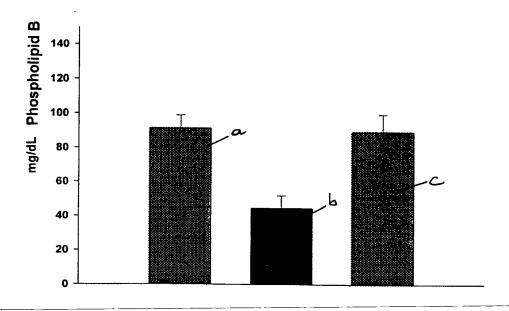


FIGURE 4

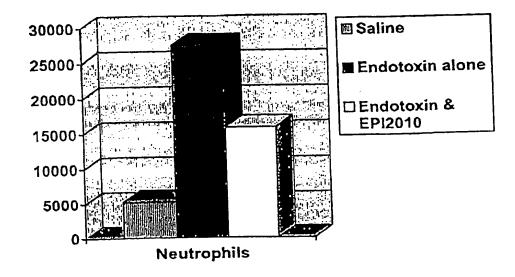


FIGURE 5

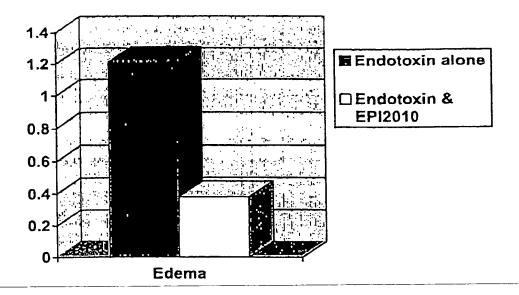


FIGURE 6

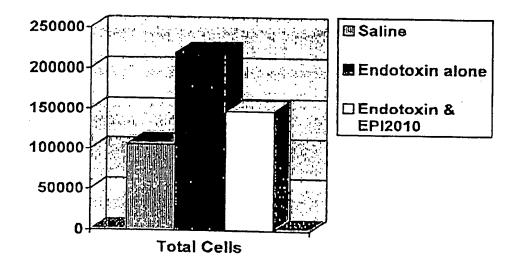


FIGURE 7

SEQUENCE LISTING

(1) GENERAL INFORMATION: (i) APPLICANT: Nyce, Jonathan W. and Hill, Jeffrey (ii) TITLE OF INVENTION: (iii) NUMBER OF SEQUENCES: 1004 (iv) CORRESPONDENCE ADDRESS: (A) ADDRESSEE: ARTER & HADDEN (B) STREET: 725 South Figueroa St. (C) CITY: Los Angeles (D) STATE: California (E) COUNTRY: USA (F) ZIP: 900071 (v) COMPUTER READABLE FORM: (A) MEDIUM TYPE: Floppy disk (B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (vi) CURRENT APPLICATION DATA: (A) APPLICATION NUMBER: (B) FILING DATE: 8-JUN-1999 (C) CLASSIFICATION: (A) APPLICATION NUMBER: US 60/088,657 (B) FILING DATE: 9-JUN-1998 (C) CLASSIFICATION: (A) APPLICATION NUMBER: US 60/088,501 (B) FILING DATE: 8-JUN-1998 (C) CLASSIFICATION: (A) APPLICATION NUMBER: US 09/093,972 (B) FILING DATE: 9-JUN-1998 (C) CLASSIFICATION: (viii) ATTORNEY/AGENT INFORMATION: (A) NAME: Amzel, Viviana (B) REGISTRATION NUMBER: 30,930 (C) REFERENCE/DOCKET NUMBER: EPI-179 (ix) TELECOMMUNICATION INFORMATION: (A) TELEPHONE: 213-430-3520 (B) TELEFAX: 213-617-9255 (C) TELEX: (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1: GATGGAGGC GGCATGGCGG G 21 (2) INFORMATION FOR SEQ ID NO:2: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

GTAG	CAGGCG GGGATGGGGG C	21
	INFORMATION FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3: PTGGGC ATCTTGCC	18
	INFORMATION FOR SEQ ID NO:4: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:	
	TTGCGG ATCTAGGC	18
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	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:	
GTGG	GCCTAG CTCTCGCC	18
	INFORMATION FOR SEQ ID NO:6: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6: GGGTAC CTGTCGGC	10
(2)	INFORMATION FOR SEQ ID NO:7: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 51 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	18
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:	
	GCCTGG AAAGCTGAGA TGGAGGCCGG CATGGCGGGC ACAGGCTGGG C 51	
(2)	INFORMATION FOR SEQ ID NO:8: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 50 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
cccc	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:	E 0
9000	GCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG	50

(2) INFORMATION FOR SEQ ID NO:9: (i) SEQUENCE CHARACTERISTICS:	
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(C) STRANDEDNESS: single	
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:	
GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGG	49
(2) INFORMATION FOR SEQ ID NO:10:	
(i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 48 base pairs (B) TYPE: nucleic acid	
(C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:</pre>	
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(2) INFORMATION FOR SEO ID NO:11:	
(i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 47 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:</pre>	
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(2) INFORMATION FOR SEQ ID NO:12:	
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(A) LENGTH: 46 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:</pre>	
GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGC	46
(2) INFORMATION FOR CEO ID NO.12.	
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(A) LENGTH: 45 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:</pre>	
GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGG	45
(2) INFORMATION FOR SEQ ID NO:14: (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 44 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	
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(2) INFORMATION FOR SEQ ID NO:15: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 43 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACA	43
(2) INFORMATION FOR SEQ ID NO:16: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 42 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:	
GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC AC (2) INFORMATION FOR SEQ ID NO:17: (i) SEQUENCE CHARACTERISTICS:	42
(A) LENGTH: 41 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC A	41
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(2) INFORMATION FOR SEQ ID NO:20: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 38 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	33
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGG	38

(2) INFORMATION FOR SEQ ID NO:21: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 37 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:21: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCG	37
(2) INFORMATION FOR SEQ ID NO:22: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 36 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGC	36
(2) INFORMATION FOR SEQ ID NO:23: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:	
-GGCGGCCTGG-AAAGCTGAGA-TGGAGGGCGG-CATGG	3.5
(2) INFORMATION FOR SEQ ID NO:24: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATG	34
(2) INFORMATION FOR SEQ ID NO:25: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CAT	22
(2) INFORMATION FOR SEQ ID NO:26: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	33
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CA	32

(2) INFORMATION FOR SEQ ID NO:27: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG C	31
(2) INFORMATION FOR SEQ ID NO:28. (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28: COCCCCTEGG AAAGCTGAGA TGGAGGGCGG	30
(2) INFORMATION FOR SEQ ID NO:29: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	29
(2) INFORMATION FOR SEQ ID NO:30: (i) SEQUENCE CHARACTERISTICS: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: GGCGGCCTGG AAAGCTGAGA TGGAGGGC	28
(2) INFORMATION FOR SEQ ID NO:31: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	27
(2) INFORMATION FOR SEQ ID NO:32: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 26 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32: GGCGGCCTGG AAAGCTGAGA TGGAGG	26

(2) INFORMATION FOR SEQ ID NO:33: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 25 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33: GGCGGCCTGG AAAGCTGAGA TGGAG	25
(2) INFORMATION FOR SEQ ID NO:34: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: GGCGGCCTGG AAAGCTGAGA	24
(2) INFORMATION FOR SEQ ID NO:35: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: GGEGGEGTGG-AAAGCTGAGA-TGG	23
(2) INFORMATION FOR SEQ ID NO:36: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36: GGCGGCCTGG AAAGCTGAGA TG	22
(2) INFORMATION FOR SEQ ID NO:37: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37: GGCGGCCTGG AAAGCTGAGA T	21
(2) INFORMATION FOR SEQ ID NO:38: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 20 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38: CGGCCTGG AAAGCTGAGA	20

	NFORMATION FOR SEQ ID NO:39: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 19 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(×	li) MOLECULE TYPE: DNA (genomic) (i) SEQUENCE DESCRIPTION: SEQ ID NO:39: CCTGG AAAGCTGAG	19
	NFORMATION FOR SEQ ID NO:40: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(x	Li) MOLECULE TYPE: DNA (genomic) Li) SEQUENCE DESCRIPTION: SEQ ID NO:40: CCTGG AAAGCTGA	18
	NFORMATION FOR SEQ ID NO:41: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 17 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(x	Li) MOLECULE TYPE: DNA (genomic) Li) SEQUENCE DESCRIPTION: SEQ ID NO:41: CCTGG AAAGCTG	17
(i () ()	NFORMATION FOR SEQ ID NO:42: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear Li) MOLECULE TYPE: DNA (genomic) Ki) SEQUENCE DESCRIPTION: SEQ ID NO:42:	
	CCTGG AAAGCT	16
) i)	NFORMATION FOR SEQ ID NO:43: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear Li) MOLECULE TYPE: DNA (genomic)	
	xi) SEQUENCE DESCRIPTION: SEQ ID NO:43: CCTGG AAAGC	15
,	NFORMATION FOR SEQ ID NO:44: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
()	ii) MOLECULE TYPE: DNA (genomic) ki) SEQUENCE DESCRIPTION: SEQ ID NO:44: CCTGG AAAG	14

	<pre>INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 13 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: GCCTGG AAA</pre>	13
	INFORMATION FOR SEQ ID NO:46:	13
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 12 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46: GCCTGG AA	12
(2)	<pre>INFORMATION FOR SEQ ID NO:47: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 11 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear</pre>	
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47: GCCTGG A	1-1
		11
	INFORMATION FOR SEQ ID NO:48: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 10 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:	
GGCGI	GCCTGG	10
	<pre>INFORMATION FOR SEQ ID NO:49: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 50 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49: CCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGGC	50
	INFORMATION FOR SEQ ID NO:50: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 49 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50: CCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGG	49

GCGG	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 48 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGG	48
(2)	<pre>INFORMATION FOR SEQ ID NO:52: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 47 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:</pre>	
GCGG	GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTG	47
(2)	<pre>INFORMATION FOR SEQ ID NO:53: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 46 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCT	46
(2)		45
(2)	INFORMATION FOR SEQ ID NO:55: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 44 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:55: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGG	44
(2)	<pre>INFORMATION FOR SEQ ID NO:56: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 43 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:56: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAG</pre>	43
~~~	JOLIGGA ANGOIGAND GOOGGOOG AIGGOOGGA (AG	43

(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57: GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CA	42
(2) INFORMATION FOR SEQ ID NO:58: (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 41 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:58: GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA C	4.1
	41
(2) INFORMATION FOR SEQ ID NO:59:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 40 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:</pre>	
GCGGCCTGGA AAGCTGAGAT GGAGGCGGC_ATGGCGGGCA	40
(2) INFORMATION FOR SEQ ID NO:60:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:</pre>	
GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGC	39
(2) INFORMATION FOR SEQ ID NO:61:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61: GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGG	38
(2) INFORMATION FOR SEQ ID NO:62:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:</pre>	
GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGG	37

(2)	<pre>INFORMATION FOR SEQ ID NO:63:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 36 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63: GCCTGGA AAGCTGAGAT GGAGGCCGC ATGGCG	36
(2)	<pre>INFORMATION FOR SEQ ID NO:64: (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 35 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear</pre>	
GCGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:64: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGC	35
(2)	<pre>INFORMATION FOR SEQ ID NO:65:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 34 base pairs      (B) TYPE: nucleic acid      (C) STRANDEDNESS: single      (D) TOPOLOGY: linear</pre>	
GCGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATGG	34
(2)	<pre>INFORMATION FOR SEQ ID NO:66:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 33 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear</pre>	
GCGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:66: GCCTGGA AAGCTGAGAT GGAGGGCGGC ATG	33
(2)	<pre>INFORMATION FOR SEQ ID NO:67:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 32 base pairs      (B) TYPE: nucleic acid      (C) STRANDEDNESS: single      (D) TOPOLOGY: linear</pre>	
GCGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:67: GCCTGGA AAGCTGAGAT GGAGGGCGGC AT	32
(2)	<pre>INFORMATION FOR SEQ ID NO:68:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 31 base pairs      (B) TYPE: nucleic acid      (C) STRANDEDNESS: single      (D) TOPOLOGY: linear</pre>	
GCGG	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68: GCCTGGA AAGCTGAGAT GGAGGGCGGC A	31

	INFORMATION FOR SEQ ID NO:69:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCCTGGA AAGCTGAGAT GGAGGGCGGC	NO:69:	30
	INFORMATION FOR SEQ ID NO:70:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCCTGGA AAGCTGAGAT GGAGGGCGG	NO:70:	29
(2)	INFORMATION FOR SEQ ID NO:71:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CCCTGGA AAGCTGAGAT GGAGGGCG	NO:71:	28
<u>(,5,)</u>	INFORMATION FOR SEQ ID NO:72:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID	NO:72:	
GCGG	CCTGGA AAGCTGAGAT GGAGGGC		27
(2)	INFORMATION FOR SEQ ID NO:73:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CCTGGA AAGCTGAGAT GGAGGG	NO:73:	26
(2)	INFORMATION FOR SEQ ID NO:74:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	NO : 74 ·	

(D) TOPOLOGY: linear

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GCGG	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:80: GCCTGGA AAGCTGAGA	19
(2)	INFORMATION FOR SEQ ID NO:81:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
GCGG	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:81: CCCTGGA AAGCTGAG	18
	INFORMATION FOR SEQ ID NO:82:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:  CCCTGGA AAGCTGA	17
(2)	INFORMATION FOR SEQ ID NO:83:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	·
GCGG	(D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:  CCTGGA AAGCTG	16
	INFORMATION FOR SEQ ID NO:84:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:	15
(2)	<pre>INFORMATION FOR SEQ ID NO:85:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:</pre>	15
	CCTGGA AAGC INFORMATION FOR SEQ ID NO:86:	14
•	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid	

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86: CCTGGA AAG	13
	INFORMATION FOR SEQ ID NO:87:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87: CCTGGA AA	12
	INFORMATION FOR SEQ ID NO:88:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
GCGG	CCTGGA A	11
(2)	<pre>INFORMATION FOR SEQ ID NO:89:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:</pre>	
GCGG		10
(2)	<pre>INFORMATION FOR SEQ ID NO:90:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 49 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear</pre>	
CGGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ'ID NO:90: CTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC	49
(2)	INFORMATION FOR SEQ ID NO:91:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 48 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
CGGC	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91: CCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGG	48
(2)	INFORMATION FOR SEQ ID NO:92: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 47 base pairs	

CGGC	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:92: CCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGG	47
(2)	<pre>INFORMATION FOR SEQ ID NO:93:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 46 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	46
(2)	<pre>INFORMATION FOR SEQ ID NO:94:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 45 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:	45
CGGC	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95: CTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGC	44
(2)	<pre>INFORMATION FOR SEQ ID NO:96:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 43 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:</pre>	
CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGG  (2) INFORMATION FOR SEQ ID NO:97:		
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:	42
(2)	INFORMATION FOR SEQ ID NO:98: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 41 base pairs	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:98: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC A	41
(2) INFORMATION FOR SEQ ID NO:99:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 40 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC	40
(2) INFORMATION FOR SEQ ID NO:100:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:100: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCA	39
(2) INFORMATION FOR SEQ ID NO:101:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 38 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:101: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGC	38
(2) INFORMATION FOR SEQ ID NO:102:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 37 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:102: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGG	37
(2) INFORMATION FOR SEQ ID NO:103:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:  CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGG	36
(2) INFORMATION FOR SEQ ID NO:104:	-
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 base pairs	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:104: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCG	35
(2) INFORMATION FOR SEQ ID NO:105:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 34 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:105: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGC	34
(2) INFORMATION FOR SEQ ID NO:106:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGG  (2) INFORMATION FOR SEQ ID NO:107:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 32 base pairs         (B) TYPE: nucleic acid	33
(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:107: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TG	32
(2) INFORMATION FOR SEQ ID NO:108:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA T	31
(2) INFORMATION FOR SEQ ID NO:109:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 30 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:109: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA	30
(2) INFORMATION FOR SEQ ID NO:110: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs	

	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110: CTGGAA AGCTGAGATG GAGGGCGGC	29
	<pre>INFORMATION FOR SEQ ID NO:111:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 28 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:</pre>	
CGGC	CTGGAA AGCTGAGATG GAGGGCGG  INFORMATION FOR SEQ ID NO:112:  (i) SEQUENCE CHARACTERISTICS:	28
	(A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:112: CTGGAA AGCTGAGATG GAGGGCG	27
	<pre>INFORMATION FOR SEQ ID NO:113:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 26 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:</pre>	
		26
	INFORMATION FOR SEQ ID NO:114:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:  CTGGAA AGCTGAGATG GAGGG	25
(2)	INFORMATION FOR SEQ ID NO:115:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:	24
(2)	INFORMATION FOR SEQ ID NO:116: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs	

(2) INFORMATION FOR SEQ ID NO:117:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:  CGGCCTGGAA AGCTGAGATG GA  (2) INFORMATION FOR SEQ ID NO:118:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:	23		
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:  CGGCCTGGAA AGCTGAGATG GA  (2) INFORMATION FOR SEQ ID NO:118:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:  CGGCCTGGAA AGCTGAGATG G  (2) INFORMATION FOR SEQ ID NO:119:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs			
(2) INFORMATION FOR SEQ ID NO:118:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:  CGGCCTGGAA AGCTGAGATG G  (2) INFORMATION FOR SEQ ID NO:119:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs			
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:  CGGCCTGGAA AGCTGAGATG G  (2) INFORMATION FOR SEQ ID NO:119:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs	21		
<ul> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:</li> <li>CGGCCTGGAA AGCTGAGATG G</li> <li>(2) INFORMATION FOR SEQ ID NO:119:</li> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 20 base pairs</li> </ul>	21		
<ul> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:</li> <li>CGGCCTGGAA AGCTGAGATG G</li> <li>(2) INFORMATION FOR SEQ ID NO:119: <ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 20 base pairs</li> </ul> </li> </ul>	21		
(2) INFORMATION FOR SEQ ID NO:119: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 20 base pairs	21		
<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 20 base pairs</li></ul>			
(B) TYPE: nucleic acid			
(C) STRANDEDNESS: single			
(D) TOPOLOGY: linear			
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:</pre>			
CCCCCCCA ACCCCACACACA	20		
(2) INFORMATION FOR SEQ ID NO:120:			
(i) SEQUENCE CHARACTERISTICS:			
<ul><li>(A) LENGTH: 19 base pairs</li><li>(B) TYPE: nucleic acid</li></ul>			
(C) STRANDEDNESS: single			
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)			
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:			
CGGCCTGGAA AGCTGAGAT			
(2) INFORMATION FOR SEQ ID NO:121:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear			
(ii) MOLECULE TYPE: DNA (genomic)			
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121: CGGCCTGGAA AGCTGAGA	18		
(2) INFORMATION FOR SEQ ID NO:122:			
12) INFORMATION FOR SECTION NOTIZET			

CGGC	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID CCTGGAA AGCTGAG	NO:122:
	INFORMATION FOR SEQ ID NO:123:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID 1	
(2)	INFORMATION FOR SEQ ID NO:124:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID INCCTGGAA AGCTG	NO:124:
	INFORMATION FOR SEQ ID NO:125:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID (CCTGGAA AGCT	NO:125:
	INFORMATION FOR SEQ ID NO:126:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID INCORPORATION:	NO:126:
	INFORMATION FOR SEQ ID NO:127:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID 10 CCTGGAA AG	NO:127:
(2)	<pre>INFORMATION FOR SEQ ID NO:128:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 11 base pairs</pre>	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:128: CGGCCTGGAA A	11
(2) INFORMATION FOR SEQ ID NO:129:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 10 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129: CGGCCTGGAA	10
(2) INFORMATION FOR SEQ ID NO:130:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 48 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:	
GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGGGC  (2) INFORMATION FOR SEQ ID NO:131:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 47 base pairs  (B) TYPE: nucleic acid	48
(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNR (conomic)	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGGG</pre>	47
(2) INFORMATION FOR SEQ ID NO:132:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 46 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single	_
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGG	46
(2) INFORMATION FOR SEQ ID NO:133:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 45 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:</pre>	
GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTG	45
(2) INFORMATION FOR SEQ ID NO:134:  (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 44 base pairs (B) TYPE: nucleic acid	

<ul><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:134: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCT	44
(2) INFORMATION FOR SEQ ID NO:135:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:135: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGC</pre>	43
(2) INFORMATION FOR SEQ ID NO:136:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GG	42
(2) INFORMATION FOR SEQ ID NO:137:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:  GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA G	41
(2) INFORMATION FOR SEQ ID NO:138:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 40 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:  GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA	40
(2) INFORMATION FOR SEQ ID NO:139:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 39 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:139: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCAC	39
(2) INFORMATION FOR SEQ ID NO:140: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 38 base pairs	

## (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:145: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGC 33 (2) INFORMATION FOR SEQ ID NO:146: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:146: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GG	32
(2) INFORMATION FOR SEQ ID NO:147:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:147:	
GGCCTGGAAA GCTGAGATGG AGGGCGGCAT G  (2) INFORMATION FOR SEQ ID NO:148:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 30 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear	31
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:148: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT	30
(2) INFORMATION FOR SEQ ID NO:149:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 29 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:149: GGCCTGGAAA GCTGAGATGG AGGGCGGCA	29
(2) INFORMATION FOR SEQ ID NO:150:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:150: GGCCTGGAAA GCTGAGATGG AGGGCGGC	28
(2) INFORMATION FOR SEQ ID NO:151:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:151: GGCCTGGAAA GCTGAGATGG AGGGCGG	27
<ul><li>(2) INFORMATION FOR SEQ ID NO:152:</li><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 26 base pairs</li></ul>	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCTGGAAA GCTGAGATGG	NO:158:	0
(2) INFORMATION FOR SEQ ID NO:159:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCTGGAAA GCTGAGATG	NO:159:	9
(2) INFORMATION FOR SEQ ID NO:160:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCTGGAAA GCTGAGAT	NO:160:	8
(2) INFORMATION FOR SEQ ID NO:161:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCTGGAAA GCTGAGA	NO:161:	7
(2) INFORMATION FOR SEQ ID NO:162:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCTGGAAA GCTGAG		. 6
(2) INFORMATION FOR SEQ ID NO:163:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 15 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID		_
GGCCTGGAAA GCTGA	1	. 5

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:164: GGCCTGGAAA GCTG	14
(2) INFORMATION FOR SEQ ID NO:165:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:165: GGCCTGGAAA GCT	13
(2) INFORMATION FOR SEQ ID NO:166:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 12 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:166: GGCCTGGAAA GC	12
(2) INFORMATION FOR SEQ ID NO:167:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:167: GGCCTGGAAA G	11
(2) INFORMATION FOR SEQ ID NO:168:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:168:	
GGCCTGGAAA  (2) INFORMATION FOR SEO ID NO:169:	10
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 47 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:  GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG GCTGGGC	47
(2) INFORMATION FOR SEQ ID NO:170: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 46 base pairs	

GCC!	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:170: TGGAAAG CTGAGATGGA GGGCGCATG GCGGGCACAG GCTGGG	46
	<pre>INFORMATION FOR SEQ ID NO:171: (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 45 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear</pre>	
GCC:	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:171: TGGAAAG CTGAGATGGA GGGCGCATG GCGGGCACAG GCTGG	45
(2)	<pre>INFORMATION FOR SEQ ID NO:172:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 44 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCC:	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172: TGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG GCTG	44
	INFORMATION FOR SEQ ID NO:173:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:173: IGGAAAG CTGAGATGGA GGGCGCATG GCGGGCACAG GCT	43
(2)	INFORMATION FOR SEQ ID NO:174:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:174: TGGAAAG CTGAGATGGA GGGCGCATG GCGGGCACAG GC	42
	INFORMATION FOR SEQ ID NO:175:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:175: TGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG G	41
(2)	INFORMATION FOR SEQ ID NO:176: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 40 base pairs	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:176: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG	40
(2) INFORMATION FOR SEQ ID NO:177:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:  GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACA	39
(2) INFORMATION FOR SEQ ID NO:178:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	39
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCAC	38
(2) INFORMATION FOR SEQ ID NO:179:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:179: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCA</pre>	37
(2) INFORMATION FOR SEQ ID NO:180:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:180: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGC</pre>	36
(2) INFORMATION FOR SEQ ID NO:181:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 35 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(11) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:181: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGG	35
<ul><li>(2) INFORMATION FOR SEQ ID NO:182:</li><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 34 base pairs</li></ul>	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:182: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGG	34
(2) INFORMATION FOR SEQ ID NO:183:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 33 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:183: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCG	<b>~</b> ~
(2) INFORMATION FOR SEQ ID NO:184:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:  GCCTGGAAAG CTGAGATGGA GGGCGGCATG GC	33
(2) INFORMATION FOR SEQ ID NO:185:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:185: GCCTGGAAAG CTGAGATGGA GGGCGGCATG G	31
(2) INFORMATION FOR SEQ ID NO:186:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 30 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA. (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:186: GCCTGGAAAG CTGAGATGGA GGGCGGCATG	30
(2) INFORMATION FOR SEQ ID NO:187:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 29 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:187: GCCTGGAAAG CTGAGATGGA GGGCGGCAT	29
<ul><li>(2) INFORMATION FOR SEQ ID NO:188:</li><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 28 base pairs</li></ul>	

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ O		28
(2) INFORMATION FOR SEQ ID NO:189:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 27 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ		
GCCTGGAAAG CTGAGATGGA GGGCGGC	10 NO. 103.	27
(2) INFORMATION FOR SEQ ID NO:190:    (i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 26 base pairs	·	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ		
GCCTGGAAAG CTGAGATGGA GGGCGG		26
(2) INFORMATION FOR SEQ ID NO:191: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 25 base pairs		
(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ		2.5
GCCIGGAAAG CIGAGAIGGA GGGCG		25
(2) INFORMATION FOR SEQ ID NO:192:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 24 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single		
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ : GCCTGGAAAG CTGAGATGGA GGGC	c) ID NO:192:	24
(2) INFORMATION FOR SEQ ID NO:193:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 23 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ		
GCCTGGAAAG CTGAGATGGA GGG		23
(2) INFORMATION FOR SEQ ID NO:194:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs		

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GCCI	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:194: TGGAAAG CTGAGATGGA GG	22
(2)	<pre>INFORMATION FOR SEQ ID NO:195:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 21 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:195:</pre>	
GCCT		21
(2)	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 20 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
GCCT	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:196: GGAAAG CTGAGATGGA	20
	INFORMATION FOR SEQ ID NO:197:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:  GGAAAG CTGAGATGG	19
	INFORMATION FOR SEQ ID NO:198:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:198: CGGAAAG CTGAGATG	18
	INFORMATION FOR SEQ ID NO:199:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:199:  CGGAAAG CTGAGAT	17
(2)	INFORMATION FOR SEQ ID NO:200: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs	

(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:205:
GCCTGGAAAG C

(2) INFORMATION FOR SEQ ID NO:206:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 10 base pairs

(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:206: GCCTGGAAAG	10
(2) INFORMATION FOR SEQ ID NO:207:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 46 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:207: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGGGC	46
(2) INFORMATION FOR SEQ ID NO:208:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 45 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:208: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGGG	45
(2) INFORMATION FOR SEQ ID NO:209:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 44 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:209:  CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGG	44
(2) INFORMATION FOR SEQ ID NO:210:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 43 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:210: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTG	43
(2) INFORMATION FOR SEQ ID NO:211:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:211:  CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CT	42
(2) INFORMATION FOR SEQ ID NO:212:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs	

(2) INFORMATION FOR SEQ ID NO:217: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:217: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCA

(2) INFORMATION FOR SEO ID NO:218:

(A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:218: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGC	35
(2) INFORMATION FOR SEQ ID NO:219:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:219:  CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGG	34
(2) INFORMATION FOR SEQ ID NO:220:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 33 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:220: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGG	33
(2) INFORMATION FOR SEQ ID NO:221:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 32 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:221: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CG	32
(2) INFORMATION FOR SEQ ID NO:222:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:222: CCTGGAAAGC TGAGATGGAG GGCGGCATGG C	31
(2) INFORMATION FOR SEQ ID NO:223:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:223: CCTGGAAAGC TGAGATGGAG GGCGGCATGG</pre>	30

	RMATION FOR SEQ ID NO:224: SEQUENCE CHARACTERISTICS: (A) LENGTH: 29 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear		
(xi) CCTGGAAAG (2) INFOF (i)	MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID C TGAGATGGAG GGCGGCATG MATION FOR SEQ ID NO:225: SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	NO:224:	29
(xi)	MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID C TGAGATGGAG GGCGGCAT	NO:225:	28
(i) (ii) (xi)	MATION FOR SEQ ID NO:226: SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID CC TGAGATGGAG GGCGGCA	NO:226:	27
	MATION FOR SEQ ID NO:227: SEQUENCE-CHARACTERISTICS:		
(xi)	(A) LENGTH: 26 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID CC TGAGATGGAG GGCGGC	NO:227:	26
(2) INFOR	MATION FOR SEQ ID NO:228:		
(ii) (xi)	SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  MOLECULE TYPE: DNA (genomic)  SEQUENCE DESCRIPTION: SEQ ID  CC TGAGATGGAG GGCGG	NO:228:	25
(i)	MATION FOR SEQ ID NO:229: SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear		
(xi)	MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID C TGAGATGGAG GGCG	NO:229:	24

(2) INFORMATION FOR SEQ ID NO:230:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 23 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:230: CCTGGAAAGC TGAGATGGAG GGC	23
(2) INFORMATION FOR SEQ ID NO:231:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:231: CCTGGAAAGC TGAGATGGAG GG	22
(2) INFORMATION FOR SEQ ID NO:232:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:232: CCTGGAAAGC TGAGATGGAG G</pre>	21
(2) INFORMATION FOR SEQ ID NO:233:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:233: CCTGGAAAGC TGAGATGGAG	20
(2) INFORMATION FOR SEQ ID NO:234:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:234:  CCTGGAAAGC TGAGATGGA	19
(2) INFORMATION FOR SEQ ID NO:235:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:235: .  CCTGGAAAGC TGAGATGG	18

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(2) INFORMATION FOR SEQ ID NO:236:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 17 base pairs (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
     (ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:236:
CCTGGAAAGC TGAGATG
                                                                              17
(2) INFORMATION FOR SEQ ID NO:237:
    (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 16 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
     (ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:237:
CCTGGAAAGC TGAGAT
                                                                              16
(2) INFORMATION FOR SEQ ID NO:238:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 15 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
     (ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:238:
CCTGGAAAGC-TGAGA-
                                                                               15
(2) INFORMATION FOR SEQ ID NO:239:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 14 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
     (ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:239:
CCTGGAAAGC TGAG
                                                                              14
(2) INFORMATION FOR SEQ ID NO:240:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 13 base pairs
           (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:240:
CCTGGAAAGC TGA
                                                                              13
(2) INFORMATION FOR SEQ ID NO:241:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 12 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
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(2) INFORMATION FOR SEQ ID NO:247: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(XI) SEQUENCE DESCRIPTION. SEQ ID NO:255:

CTGGAAAGCT GAGATGGAGG GCGGCATGGC GGGC

(2) INFORMATION FOR SEQ ID NO:256:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(XI) SEQUENCE DESCRIPTION: SEO ID NO:256:

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:256:
CTGGAAAGCT GAGATGGAGG GCGGCATGGC GGG
33

(2) INFORMATION FOR SEQ ID NO:257:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:257:
CTGGAAAGCT GAGATGGAGG GCGCATGGC GG 32

(2) INFORMATION FOR SEQ ID NO:258:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 31 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:258:
CTGGAAAGCT GAGATGGAGG GCGCATGGC G 31

(2) INFORMATION FOR SEQ ID NO:259:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:259: CTGGAAAGCT GAGATGGAGG GCGGCATGGC	30
(2) INFORMATION FOR SEQ ID NO:260:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:260:  CTGGAAAGCT GAGATGGAGG GCGGCATGG	29
(2) INFORMATION FOR SEQ ID NO:261:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:261: CTGGAAAGCT GAGATGGAGG GCGGCATG	28
(2) INFORMATION FOR SEQ ID NO:262:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:262:  CTGGAAAGCT GAGATGGAGG GCGGCAT	 27
(2) INFORMATION FOR SEQ ID NO:263:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 26 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:263: CTGGAAAGCT GAGATGGAGG GCGGCA	26
(2) INFORMATION FOR SEQ ID NO:264:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:264: CTGGAAAGCT GAGATGGAGG GCGC	25
(2) INFORMATION FOR SEQ ID NO:265:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 24 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

	xi) SEQUENCE DESCRIPTION: SEQ ID NO:265: AAGCT GAGATGGAGG GCGG	24
(. (:	NFORMATION FOR SEQ ID NO:266:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID NO:266:  AAGCT GAGATGGAGG GCG	23
	NFORMATION FOR SEQ ID NO:267:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(:	ii) MOLECULE TYPE: DNA (genomic) xi) SEQUENCE DESCRIPTION: SEQ ID NO:267: AAGCT GAGATGGAGG GC	22
(: (;	NFORMATION FOR SEQ ID NO:268:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID NO:268:  AAGCT GAGATGGAGG G	21
(; ;)	NFORMATION FOR SEQ ID NO:269:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID NO:269:  AAGCT GAGATGGAGG	20
(. (;	NFORMATION FOR SEQ ID NO:270:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID NO:270:	
		19
	NFORMATION FOR SEQ ID NO:271:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:271: CTGGAAAGCT GAGATGGA	18
(2) INFORMATION FOR SEQ ID NO:272:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:272: CTGGAAAGCT GAGATGG	17
(2) INFORMATION FOR SEQ ID NO:273:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:273: CTGGAAAGCT GAGATG	16
(2) INFORMATION FOR SEQ ID NO:274:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (XI) SEQUENCE DESCRIPTION: SEQ ID NO:274:	
CTGGAAAGCT GAGAT	15
<pre>(2) INFORMATION FOR SEQ ID NO:275:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:275:</pre>	
CTGGAAAGCT GAGA	14
(2) INFORMATION FOR SEQ ID NO:276:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:276:	
CTGGAAAGCT GAG	13
(2) INFORMATION FOR SEQ ID NO:277:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 12 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:277: CTGGAAAGCT GA	12
(2) INFORMATION FOR SEQ ID NO:278:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic.acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:278:  CTGGAAAGCT G	11
(2) INFORMATION FOR SEQ ID NO:279:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:279:	
CTGGAAAGCT	10
(2) INFORMATION FOR SEQ ID NO:280:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 44 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:280: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT GGGC	44
(2) INFORMATION FOR SEQ ID NO:281:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:281:	4.7
TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT GGG	43
(2) INFORMATION FOR SEQ ID NO:282:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 42 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:282:	
TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT GG	42
(2) INFORMATION FOR SEQ ID NO:283:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 41 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:283: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT G	41
(2) INFORMATION FOR SEQ ID NO:284:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 40 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:284: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT	40
(2) INFORMATION FOR SEQ ID NO:285:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 39 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:285: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGC	39
(2) INFORMATION FOR SEQ ID NO:286:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 38 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:286: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGG	38
(2) INFORMATION FOR SEQ ID NO:287:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 37 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:287: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAG	37
(2) INFORMATION FOR SEQ ID NO:288:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:288: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACA	36
(2) INFORMATION FOR SEQ ID NO:289:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 35 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	36

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## (2) INFORMATION FOR SEQ ID NO:294: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs

TGGAAAGCTG AGATGGAGGG CGGCATGGCG G

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:294: TGGAAAGCTG AGATGGAGGG CGGCATGGCG

(2) INFORMATION FOR SEQ ID NO:295:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:295: TGGAAAGCTG AGATGGAGGG CGGCATGGC	29
(2) INFORMATION FOR SEQ ID NO:296:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:296: TGGAAAGCTG AGATGGAGGG CGGCATGG	28
(2) INFORMATION FOR SEQ ID NO:297:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:297: TGGAAAGCTG AGATGGAGGG CGGCATG	27
(2) INFORMATION FOR SEQ ID NO:298:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (Xi) SEQUENCE DESCRIPTION: SEQ ID NO:298:	
TGGAAAGCTG AGATGGAGGG CGGCAT	26
(2) INFORMATION FOR SEQ ID NO:299:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:299: TGGAAAGCTG AGATGGAGGG CGGCA	25
(2) INFORMATION FOR SEQ ID NO:300:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 24 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:300: TGGAAAGCTG AGATGGAGGG CGGC	24
(2) INFORMATION FOR SEQ ID NO:301:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	_

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:301: TGGAAAGCTG AGATGGAGGG CGG	23
(2) INFORMATION FOR SEQ ID NO:302:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 22 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:302: TGGAAAGCTG AGATGGAGGG CG	22
(2) INFORMATION FOR SEQ ID NO:303:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:303: TGGAAAGCTG AGATGGAGGG C	21
(2) INFORMATION FOR SEQ ID NO:304:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:304: TGGAAAGCTG AGATGAGGG	20
(2) INFORMATION FOR SEQ ID NO:305:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:305: TGGAAAGCTG AGATGGAGG	19
(2) INFORMATION FOR SEQ ID NO:306:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:306: TGGAAAGCTG AGATGGAG	18

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(2) INFORMATION FOR SEQ ID NO:307: (i) SEQUENCE CHARACTERISTICS:

(2) INFORMATION FOR SEQ ID NO:313: (i) SEQUENCE CHARACTERISTICS:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:312:

(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

TGGAAAGCTG AG

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:313: TGGAAAGCTG A	11
(2) INFORMATION FOR SEQ ID NO:314:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 10 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:314: TGGAAAGCTG	10
(2) INFORMATION FOR SEQ ID NO:315:	10
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:315:  GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACAGGCTG GGC	43
(2) INFORMATION FOR SEQ ID NO:316:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 42 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:316:	
GGAAAGCTGA GATGGAGGCC GGCATGGCGG GCACAGGCTG GG	42
(2) INFORMATION FOR SEQ ID NO:317:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:317:	
GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACAGGCTG G	41
(2) INFORMATION FOR SEQ ID NO:318:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 40 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:318: GGAAAGCTGA GATGGAGGC GGCATGGCGG GCACAGGCTG	. 40
(2) INFORMATION FOR SEO ID NO:319:	.40
<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 39 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>	
(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:319: GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACAGGCT	39
(2) INFORMATION FOR SEQ ID NO:320:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 38 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:320: GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACAGGC	20
	38
(2) INFORMATION FOR SEQ ID NO:321:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 37 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:321: GGAAAGCTGA GATGGAGGC GGCATGGCGG GCACAGG	37
(2) INFORMATION FOR SEQ ID NO:322:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs	
(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:322: GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACAG	36
(2) INFORMATION FOR SEQ ID NO:323:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 35 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:323:	
GGAAAGCTGA GATGGAGGGC GGCATGGCGG GCACA	35
(2) INFORMATION FOR SEQ ID NO:324:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:324: GGAAAGCTGA GATGGAGGC GGCATGGCGG GCAC	34
(2) INFORMATION FOR SEQ ID NO:325:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	-

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:325: GGAAAGCTGA GATGGAGGC GGCATGGCGG GCA	33
(2) INFORMATION FOR SEQ ID NO:326:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:326:  GGAAAGCTGA GATGGAGGGC GGCATGGCGG GC	32
(2) INFORMATION FOR SEQ ID NO:327:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:327: GGAAAGCTGA GATGGAGGGC GGCATGGCGG G	31
(2) INFORMATION FOR SEQ ID NO:328:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 30 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:328: GGAAAGCTGA GATGGAGGGC GGCATGGCGG	30
(2) INFORMATION FOR SEQ ID NO:329:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:329:  GGAAAGCTGA GATGGAGGGC GGCATGGCG	29
(2) INFORMATION FOR SEQ ID NO:330:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:330:  GGAAAGCTGA GATGGAGGGC GGCATGGC	28
(2) INFORMATION FOR SEQ ID NO:331:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:331: GGAAAGCTGA GATGGAGGC GGCATGG	27	
(2) INFORMATION FOR SEQ ID NO:332:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:332:  GGAAAGCTGA GATGGAGGGC GGCATG	26	
(2) INFORMATION FOR SEQ ID NO:333:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:333:  GGAAAGCTGA GATGGAGGGC GGCAT	25	
(2) INFORMATION FOR SEQ ID NO:334:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:334:		
GGAAAGCTGA GATGGAGGGC GGCA	24	
(2) INFORMATION FOR SEQ ID NO:335:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:335:		
GGAAAGCTGA GATGGAGGGC GGC	23	
(2) INFORMATION FOR SEQ ID NO:336:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:336:  GGAAAGCTGA GATGGAGGGC GG	22	
(2) INFORMATION FOR SEQ ID NO:337:		
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)		

	i) SEQUENCE DESCRIPTION: SEQ ID NO:337: CTGA GATGGAGGGC G	21
(i. (x:	FORMATION FOR SEQ ID NO:338:  i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  i) MOLECULE TYPE: DNA (genomic) i) SEQUENCE DESCRIPTION: SEQ ID NO:338: CTGA GATGGAGGGC	20
(i) SEC (i: (x:	FORMATION FOR SEQ ID NO:339: QUENCE CHARACTERISTICS: (A) LENGTH: 19 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear i) MOLECULE TYPE: DNA (genomic) i) SEQUENCE DESCRIPTION: SEQ ID NO:339: CTGA GATGGAGGG	19
(2) INI (: (i: (x:	FORMATION FOR SEQ ID NO:340: i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear i) MOLECULE TYPE: DNA (genomic) i) SEQUENCE DESCRIPTION: SEQ ID NO:340: CTGA GATGGAGG	18
(i: (xi) SI	FORMATION FOR SEQ ID NO:341: i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 17 base pairs    (B) TYPE: nucleic acid    (C) STRANDEDNESS: single    (D) TOPOLOGY: linear i) MOLECULE TYPE: DNA (genomic) EQUENCE DESCRIPTION: SEQ ID NO:341: CTGA GATGGAG	17
(i: (x:	FORMATION FOR SEQ ID NO:342:  i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  i) MOLECULE TYPE: DNA (genomic) i) SEQUENCE DESCRIPTION: SEQ ID NO:342: CTGA GATGGA	1.5
(2) INI (:	CTGA GATGGA  FORMATION FOR SEQ ID NO:343:  i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  i) MOLECULE TYPE: DNA (genomic)	16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:349: GAAAGCTGAG ATGGAGGGGG GCATGGCGGG CACAGGCTGG GC	42
(2) INFORMATION FOR SEQ ID NO:350:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:350:  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAGGCTGG G	
	41
(2) INFORMATION FOR SEQ ID NO:351:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 40 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:351: GAAAGCTGAG ATGGAGGGGG GCATGGCGGG CACAGGCTGG	40
(2) INFORMATION FOR SEQ ID NO:352:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:352: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAGGCTG</pre>	39
(2) INFORMATION FOR SEQ ID NO:353:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:353: GAAAGCTGAG ATGGAGGGC GCATGGCGGG CACAGGCT	38
(2) INFORMATION FOR SEQ ID NO:354:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:354:</pre>	
GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAGGC	37
(2) INFORMATION FOR SEQ ID NO:355:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
,, Ditt (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:355: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAGG	36
(2) INFORMATION FOR SEQ ID NO:356:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 35 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:356: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAG	35
(2) INFORMATION FOR SEQ ID NO:357:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:357:  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACA	34
(2) INFORMATION FOR SEQ ID NO:358:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:358:  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CAC	
(2) INFORMATION FOR SEQ ID NO:359:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:359:	33
GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CA  (2) INFORMATION FOR SEQ ID NO:360:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:360: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG C	32
(2) INFORMATION FOR SEQ ID NO:361:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	31

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:361: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG	30
(2) INFORMATION FOR SEQ ID NO:362:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:362:  GAAAGCTGAG ATGGAGGGCG GCATGGCGG	29
(2) INFORMATION FOR SEQ ID NO:363:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:363:  GAAAGCTGAG ATGGAGGGCG GCATGGCG	28
(2) INFORMATION FOR SEQ ID NO:364:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:364:  GAAAGCTGAG ATGGAGGGCG GCATGGC	27
(2) INFORMATION FOR SEQ ID NO:365:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:365:  GAAAGCTGAG ATGGAGGGCG GCATGG	26
(2) INFORMATION FOR SEQ ID NO:366:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:366:  GAAAGCTGAG ATGGAGGGCG GCATG	25
(2) INFORMATION FOR SEQ ID NO:367:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:367: GAAAGCTGAG ATGGAGGGCG GCAT	24
(2) INFORMATION FOR SEQ ID NO:368:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:368:  GAAAGCTGAG ATGGAGGGCG GCA	23
(2) INFORMATION FOR SEQ ID NO:369:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:369: GAAAGCTGAG ATGGAGGGCG GC	22
(2) INFORMATION FOR SEQ ID NO:370:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLEGULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:370:	22
GAAAGCTGAG ATGGAGGGCG G	21
(2) INFORMATION FOR SEQ ID NO:371:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:371: GAAAGCTGAG ATGGAGGGCG	20
(2) INFORMATION FOR SEQ ID NO:372:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:373:	20
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:372: GAAAGCTGAG ATGGAGGGC	19
(2) INFORMATION FOR SEQ ID NO:373:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:373: GAAAGCTGAG ATGGAGGG	18
(2) INFORMATION FOR SEQ ID NO:374:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:374:  GAAAGCTGAG ATGGAGG	17
(2) INFORMATION FOR SEQ ID NO:375:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:375:	16
GAAAGCTGAG ATGGAG	16
(2) INFORMATION FOR SEQ ID NO:376:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA. (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:376:  GAAAGCTGAG ATGGA	15
(2) INFORMATION FOR SEQ ID NO:377:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:377:  GAAAGCTGAG ATGG	14
(2) INFORMATION FOR SEQ ID NO:378:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:378:  GAAAGCTGAG ATG	13
(2) INFORMATION FOR SEQ ID NO:379:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:385: AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTG	38
(2) INFORMATION FOR SEQ ID NO:386:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:386:  AAAGCTGAGA TGGAGGGGGG CATGGCGGGC ACAGGCT	37
(2) INFORMATION FOR SEQ ID NO:387:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 36 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:387: AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGC	36
(2) INFORMATION FOR SEQ ID NO:388: (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 35 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:388:  AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGG	35
	33
(2) INFORMATION FOR SEQ ID NO:389:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 34 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:389:	
AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAG	34
(2) INFORMATION FOR SEQ ID NO:390:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:390: AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACA	33
(2) INFORMATION FOR SEQ ID NO:391:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:397: AAAGCTGAGA TGGAGGGCGG CATGGC	26
(2) INFORMATION FOR SEQ ID NO:398:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:398:  AAAGCTGAGA TGGAGGGCGG CATGG	25
(2) INFORMATION FOR SEQ ID NO:399:	23
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 24 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:399: AAAGCTGAGA TGGAGGGCGG CATG	24
(2) INFORMATION FOR SEQ ID NO:400:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:400:  AAAGCTGAGA TGGAGGGCGG CAT	
	23
(2) INFORMATION FOR SEQ ID NO:401:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:401:  AAAGCTGAGA TGGAGGGCGG CA	22
(2) INFORMATION FOR SEQ ID NO:402:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:402:  AAAGCTGAGA TGGAGGGCGG C	21
(2) INFORMATION FOR SEQ ID NO:403:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 20 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
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AAAGCTGAGA TGGAGGGC (2) INFORMATION FOR SEQ ID NO: 406: (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:406: AAAGCTGAGA TGGAGGG (2) INFORMATION FOR SEQ ID NO:407: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:407: AAAGCTGAGA TGGAGG (2) INFORMATION FOR SEQ ID NO:408: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEO ID NO:408:

17 16 AAAGCTGAGA TGGAG 15 (2) INFORMATION FOR SEQ ID NO:409: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 base pairs(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)

(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:415: AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGG	39
(2) INFORMATION FOR SEQ ID NO:416:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 38 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:416:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGG	38
(2) INFORMATION FOR SEQ ID NO:417:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 37 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:417:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTG	37
(2) INFORMATION FOR SEQ ID NO:418:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:418: AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCT	36
(2) INFORMATION FOR SEQ ID NO:419:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 35 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:419:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGC	35
(2) INFORMATION FOR SEQ ID NO:420:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 34 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:420:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGG	34
(2) INFORMATION FOR SEQ ID NO:421:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS:.single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	<b>3</b> 4

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:421: AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAG	33
(2) INFORMATION FOR SEQ ID NO:422:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:422:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CA	32
(2) INFORMATION FOR SEQ ID NO:423:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 31 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:423:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA C	31
(2) INFORMATION FOR SEQ ID NO:424:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:424:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA	30
(2) INFORMATION FOR SEQ ID NO:425:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:425:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGC	29
(2) INFORMATION FOR SEQ ID NO:426:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:426:	
AAGCTGAGAT GGAGGGCGGC ATGGCGGG  (2) INFORMATION FOR SEQ ID NO:427:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 27 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	28

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:438: AAGCTGAGAT GGAGGG

AAGCTGAGAT GGAGGG

(2) INFORMATION FOR SEQ ID NO:439:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:445: AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC	39
(2) INFORMATION FOR SEQ ID NO:446:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:446:  AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGG	
	38
(2) INFORMATION FOR SEQ ID NO:447:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:447:  AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGG	37
(2) INFORMATION FOR SEQ ID NO:448:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:448:  AGCTGAGATG GAGGGCGGCA TGGCGGCCAC AGGCTG	36
(2) INFORMATION FOR SEQ ID NO:449:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 35 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:449:	
AGCTGAGATG GAGGGCGCA TGGCGGGCAC AGGCT	35
(2) INFORMATION FOR SEQ ID NO:450:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:450: AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGC	34
(2) INFORMATION FOR SEQ ID NO:451:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:457: AGCTGAGATG GAGGGCGGCA TGGCGGG	27
(2) INFORMATION FOR SEQ ID NO:458:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:458:  AGCTGAGATG GAGGGCGGCA TGGCGG	26
(2) INFORMATION FOR SEQ ID NO:459:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:459: AGCTGAGATG GAGGGCGGCA TGGCG	25
(2) INFORMATION FOR SEQ ID NO:460:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:460:  AGCTGAGATG GAGGGCGGCA TGGC	24
(2) INFORMATION FOR SEQ ID NO:461:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:461: AGCTGAGATG GAGGGCGGCA TGG	23
(2) INFORMATION FOR SEQ ID NO:462:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:462: AGCTGAGATG GAGGGCGGCA TG	22
(2) INFORMATION FOR SEQ ID NO:463:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 21 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:469: AGCTGAGATG GAGGG	15
(2) INFORMATION FOR SEQ ID NO:470:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 14 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:470: AGCTGAGATG GAGG	14
(2) INFORMATION FOR SEQ ID NO:471:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:471:  AGCTGAGATG GAG	13
(2) INFORMATION FOR SEQ ID NO:472:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:472:  AGCTGAGATG GA	13
(2) INFORMATION FOR SEQ ID NO:473:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:473:  AGCTGAGATG G	11
(2) INFORMATION FOR SEQ ID NO:474:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:474:  AGCTGAGATG	10
(2) INFORMATION FOR SEQ ID NO:475:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	10

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BNSDOCID: <WO___9963938A2_I_>

GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGC

(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(2) INFORMATION FOR SEQ ID NO:481: (i) SEQUENCE CHARACTERISTICS:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:481: GCTGAGATGG AGGGCGGCAT GGCGGGCACA GG	32
(2) INFORMATION FOR SEQ ID NO:482:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:482:  GCTGAGATGG AGGGCGGCAT GGCGGGCACA G	31
(2) INFORMATION FOR SEQ ID NO:483:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 30 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:483: GCTGAGATGG AGGGCGGCAT GGCGGGCACA	30
(2) INFORMATION FOR SEQ ID NO:484:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:484:  GCTGAGATGG AGGGCGGCAT GGCGGGCAC	29
(2) INFORMATION FOR SEQ ID NO:485:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:485: GCTGAGATGG AGGGCGGCAT GGCGGGCA	28
(2) INFORMATION FOR SEQ ID NO:486:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:486: GCTGAGATGG AGGGCGGCAT GGCGGGC	-
(2) INFORMATION FOR SEQ ID NO:487:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	27

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:504:
CTGAGATGGA GGGCGGCATG GCGGGCACAG GCTGGGC
(2) INFORMATION FOR SEQ ID NO:505:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs

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(D) TOPOLOGY: linear

(B) TYPE: nucleic acid

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic)	
	EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGGCACAG GCTGG	 36
(i) S	ATION FOR SEQ ID NO:506: EQUENCE CHARACTERISTICS: (A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic)	
	EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGCACAG GCTGG	35
(i) Si (ii) M( (xi) Si	ATION FOR SEQ ID NO:507: EQUENCE CHARACTERISTICS: (A) LENGTH: 34 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic) EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGGCACAG GCTG	34
(i) Si (ii) M( (xi) Si	ATION FOR SEQ ID NO:508: EQUENCE CHARACTERISTICS: (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic) EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGGCACAG GCT	33
(i) Si (ii) M( (xi) Si	ATION FOR SEQ ID NO:509: EQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic) EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGGCACAG GC	32
(i) S: (ii) M( (xi) S:	ATION FOR SEQ ID NO:510: EQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear OLECULE TYPE: DNA (genomic) EQUENCE DESCRIPTION: SEQ ID GGGCGGCATG GCGGGCACAG G	31

(2) INFORMATION FOR SEQ ID NO:511:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 30 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:511: CTGAGATGGA GGGCGCATG GCGGGCACAG	30
(2) INFORMATION FOR SEQ ID NO:512:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 29 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:512: CTGAGATGGA GGGCGCATG GCGGGCACA	29
(2) INFORMATION FOR SEQ ID NO:513:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:513:  CTGAGATGGA GGGGGCATG GCGGGCAC	28
(2) INFORMATION FOR SEQ ID NO:514:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:514:	20
CTGAGATGGA GGGCGCATG GCGGGCA  (2) INFORMATION FOR SEQ ID NO:515:         (i) SEQUENCE CHARACTERISTICS:	27
(2) INFORMATION FOR SEQ ID NO:516:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)	

CTG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:516: AGATGGA GGGCGGCATG GCGGG	25
(2)	INFORMATION FOR SEQ ID NO:517:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:517:  AGATGGA GGGCGGCATG GCGG	24
(2)	<pre>INFORMATION FOR SEQ ID NO:518:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 23 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CTG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:518: AGATGGA GGGCGGCATG GCG	23
	INFORMATION FOR SEQ ID NO:519:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:519: AGATGGA GGGCGGCATG GC	22
	INFORMATION FOR SEQ ID NO:520:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:520:  AGATGGA GGGCGGCATG G	21
(2) CTG	INFORMATION FOR SEQ ID NO:521:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:521:  AGATGGA GGGCGGCATG	20
	<pre>INFORMATION FOR SEQ ID NO:522:   (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 19 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear   (ii) MOLECULE TYPE: DNA (genomic)</pre>	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:528: CTGAGATGGA GGG	13		
(2) INFORMATION FOR SEQ ID NO:529:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 12 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:529: CTGAGATGGA GG	12		
(2) INFORMATION FOR SEQ ID NO:530:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:530:			
CTGAGATGGA G	11		
(2) INFORMATION FOR SEQ ID NO:531:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:531:			
CTGAGATGGA	10		
(2) INFORMATION FOR SEQ ID NO:532:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 36 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:532:			
TGAGATGGAG GGCGCATGG CGGGCACAGG CTGGGC	36		
(2) INFORMATION FOR SEQ ID NO:533:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 35 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:533:			
TGAGATGGAG GGCGCATGG CGGGCACAGG CTGGG 35			
(2) INFORMATION FOR SEQ ID NO:534:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)			

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:534: TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGG	34
(2) INFORMATION FOR SEQ ID NO:535:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:535: TGAGATGGAG GGCGGCATGG CGGGCACAGG CTG	33
(2) INFORMATION FOR SEQ ID NO:536:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 32 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:536: TGAGATGGAG GGCGGCATGG CGGGCACAGG CT	32
(2) INFORMATION FOR SEQ ID NO:537:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE_TYPE:_DNA_(genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:537:	
TGAGATGGAG GGCGCATGG CGGGCACAGG C	31
(2) INFORMATION FOR SEQ ID NO:538:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:538:  TGAGATGGAG GGCGGCATGG CGGGCACAGG	30
(2) INFORMATION FOR SEQ ID NO:539:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 29 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:539: TGAGATGGAG GGCGGCATGG CGGGCACAG	29
(2) INFORMATION FOR SEQ ID NO:540:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:540: TGAGATGGAG GGCGGCATGG CGGGCACA	28
(2) INFORMATION FOR SEQ ID NO:541:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:541: TGAGATGGAG GGCGGCATGG CGGGCAC	27
(2) INFORMATION FOR SEQ ID NO:542:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:542: TGAGATGGAG GGCGGCATGG CGGGCA	26
(2) INFORMATION FOR SEQ ID NO:543:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:543: TGAGATGGAG GGCGGCATGG CGGCC	25
(2) INFORMATION FOR SEQ ID NO:544:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:544:  TGAGATGGAG GGCGGCATGG CGGG	24
(2) INFORMATION FOR SEQ ID NO:545:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:545: TGAGATGGAG GGCGGCATGG CGG	23
(2) INFORMATION FOR SEQ ID NO:546:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:564: GAGATGGAGG GCGGCATGGC GGGCACAGGC	30
(2) INFORMATION FOR SEQ ID NO:565:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:565:  GAGATGGAGG GCGGCATGGC GGGCACAGG	29
(2) INFORMATION FOR SEQ ID NO:566:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:566: GAGATGGAGG GCGCATGGC GGGCACAG	28
(2) INFORMATION FOR SEQ ID NO:567:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:567:  GAGATGGAGG GCGGCATGGC GGGCACA	27
(2) INFORMATION FOR SEQ ID NO:568:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:568:  GAGATGGAGG GCGGCATGGC GGGCAC	26
(2) INFORMATION FOR SEQ ID NO:569:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:569: GAGATGGAGG GCGGCATGGC GGGCA	25
(2) INFORMATION FOR SEQ ID NO:570:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	23

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(A) LENGTH: 19 base pairs (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:575: GAGATGGAGG GCGGCATGG

(2) INFORMATION FOR SEQ ID NO:576:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

GAGA	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:576: ATGGAGG GCGGCATG	18
	INFORMATION FOR SEQ ID NO:577:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:577: ATGGAGG GCGGCAT	17
	INFORMATION FOR SEQ ID NO:578:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:578: ATGGAGG GCGGCA	16
	INFORMATION FOR SEQ ID NO:579:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:579: ATGGAGG GCGC	15
(2)	INFORMATION FOR SEQ ID NO:580:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:580:  ATGGAGG GCGG	14
(2)	INFORMATION FOR SEQ ID NO:581:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:581:  ATGGAGG GCG	13
(2)	<pre>INFORMATION FOR SEQ ID NO:582:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 12 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:582: GAGATGGAGG GC	12
(2) INFORMATION FOR SEQ ID NO:583:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:583:  GAGATGGAGG G	11
(2) INFORMATION FOR SEQ ID NO:584:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:584:	
GAGATGGAGG	10
(2) INFORMATION FOR SEQ ID NO:585:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:585: AGATGGAGGG CGGCATGGCG GGCACAGGCT GGGC	34
(2) INFORMATION FOR SEQ ID NO:586:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:586:  AGATGGAGGG CGGCATGGCG GGCACAGGCT GGG	22
(2) INFORMATION FOR SEQ ID NO:587:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	33
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:587: AGATGGAGGG CGGCATGGCG GGCACAGGCT GG	32
(2) INFORMATION FOR SEQ ID NO:588:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:588: AGATGGAGGG CGGCATGGCG GGCACAGGCT G	31
(2) INFORMATION FOR SEQ ID NO:589:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:589:	
AGATGGAGGG CGGCATGGCG GGCACAGGCT	30
(2) INFORMATION FOR SEQ ID NO:590:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:590: AGATGGAGGG CGGCATGGCG GGCACAGGC	29
(2) INFORMATION FOR SEQ ID NO:591:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 28 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:591:	
AGATGGAGGG CGGCATGGCG GGCACAGG	28
(2) INFORMATION FOR SEQ ID NO:592:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:592:  AGATGGAGGG CGGCATGGCG GGCACAG	27
(2) INFORMATION FOR SEQ ID NO:593:     (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 26 base pairs      (B) TYPE: nucleic acid      (C) STRANDEDNESS: single      (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:593: AGATGGAGGG CGGCATGGCG GGCACA	26
(2) INFORMATION FOR SEQ ID NO:594: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 25 base pairs	

- (B) TYPE: nucleic acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear
  (ii) MOLECULE TYPE: DNA (genomic)

## (2) INFORMATION FOR SEQ ID NO:600:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:600: AGATGGAGGG CGGCATGGC	19
(2) INFORMATION FOR SEQ ID NO:601:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:601:  AGATGGAGGG CGGCATGG	18
(2) INFORMATION FOR SEQ ID NO:602:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:602: AGATGGAGGG CGGCATG	17
(2) INFORMATION FOR SEQ ID NO:603:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:603:  AGATGGAGGG CGGCAT	16
(2) INFORMATION FOR SEQ ID NO:604:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:604: AGATGGAGGG CGGCA	15
(2) INFORMATION FOR SEQ ID NO:605:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:605: AGATGGAGGG CGGC	14
(2) INFORMATION FOR SEQ ID NO:606:    (i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 13 base pairs    (B) TYPE: nucleic acid    (C) STRANDEDNESS: single    (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)	

(i) SEQUENCE CHARACTERISTICS:

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single

(xi) SEQUENCE DESCRIPTION: SEQ ID GATGGAGGGC GGCATGGCGG GCACAGGCTG G	NO:612:
(2) INFORMATION FOR SEQ ID NO:613:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 30 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GATGGAGGGC GGCATGGCGG GCACAGGCTG	NO:613:
(2) INFORMATION FOR SEQ ID NO:614:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECUE TYPE: DNA (genomic)	NO. 614
(xi) SEQUENCE DESCRIPTION: SEQ ID GATGGAGGGC GGCATGGCGG GCACAGGCT	NO:614:
(2) INFORMATION FOR SEQ ID NO:615:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS:.single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GATGGAGGGC GGCATGGCGG GCACAGGC	NO:615:
(2) INFORMATION FOR SEQ ID NO:616:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GATGGAGGGC GGCATGGCGG GCACAGG	NO:616:
(2) INFORMATION FOR SEQ ID NO:617:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 26 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GATGGAGGGC GGCATGGCGG GCACAG	NO:617:
(2) INFORMATION FOR SEQ ID NO:618:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

GATG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:624: GAGGGC GGCATGGCG	19
	INFORMATION FOR SEQ ID NO:625:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:625: GAGGGC GGCATGGC	18
	INFORMATION FOR SEQ ID NO:626:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:626: GAGGGC GGCATGG	17
	INFORMATION FOR SEQ ID NO:627:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:627:  GAGGGC GGCATG	16
	INFORMATION FOR SEQ ID NO:628:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:628: GAGGGC GGCAT	<b>1</b> 5
	INFORMATION FOR SEQ ID NO:629:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:629: GAGGGC GGCA	14
(2)	INFORMATION FOR SEQ ID NO:630:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:636: ATGGAGGCCG GCATGGCGGG CACAGGCTGG	30
(2) INFORMATION FOR SEQ ID NO:637:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:637:  ATGGAGGGCG GCATGGCGGG CACAGGCTG	29
(2) INFORMATION FOR SEQ ID NO:638:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:638:  ATGGAGGGCG GCATGGCGGG CACAGGCT	28
(2) INFORMATION FOR SEQ ID NO:639:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:639: ATGGAGGGCG GCATGGCGGG CACAGGC	27
(2) INFORMATION FOR SEQ ID NO:640:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 26 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:640: ATGGAGGGCG GCATGGCGGG CACAGG	26
(2) INFORMATION FOR SEQ ID NO:641:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:641: ATGGAGGGCG GCATGGCGGG CACAG	25
(2) INFORMATION FOR SEQ ID NO:642:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

ATGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:642: BAGGGCG GCATGGCGGG CACA	24
	<pre>INFORMATION FOR SEQ ID NO:643:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 23 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:643: GAGGGCG GCATGGCGGG CAC</pre>	23
(2)	INFORMATION FOR SEQ ID NO:644:	
	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 22 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:644:</li> </ul>	
ATGG	AGGGCG GCATGGCGGG CA	22
	<pre>INFORMATION FOR SEQ ID NO:645:    (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 21 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear        (ii) MOLECULE TYPE: DNA (genomic)</pre>	
ATGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:645: AGGGCG GCATGGCGGG C	21
(2)	<pre>INFORMATION FOR SEQ ID NO:646:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:646:</pre>	
ATGG	AGGGCG GCATGGCGGG	20
(2)	<pre>INFORMATION FOR SEQ ID NO:647:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 19 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)</pre>	
ATGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:647: AGGGCG GCATGGCGG	19
(2)	INFORMATION FOR SEQ ID NO:648:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	

ATGGAGGGCG GCA

(2) INFORMATION FOR SEQ ID NO:654:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 12 base pairs
 (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:653:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:660: TGGAGGGCGG CATGGCGGGC ACAGGCTG	28
(2) INFORMATION FOR SEQ ID NO:661:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:661: TGGAGGGCGG CATGGCGGGC ACAGGCT	27
(2) INFORMATION FOR SEQ ID NO:662:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 26 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:662: TGGAGGGCGG CATGGCGGGC ACAGGC	26
(2) INFORMATION FOR SEQ ID NO:663:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:663: TGGAGGGCGG CATGGCGGGC ACAGG	25
(2) INFORMATION FOR SEQ ID NO:664:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:664: TGGAGGGCGG CATGGCGGGC ACAG	24
(2) INFORMATION FOR SEQ ID NO:665:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 23 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:665: TGGAGGGCGG CATGGCGGGC ACA	23
(2) INFORMATION FOR SEQ ID NO:666:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

# TGGAGGGCGG CATGGCGGGC (2) INFORMATION FOR SEQ ID NO:669: TGGAGGGCGG CATGGCGGG (2) INFORMATION FOR SEQ ID NO:670: (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:670: TGGAGGGCGG CATGGCGG 18 (2) INFORMATION FOR SEQ ID NO:671: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 17 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:671: TGGAGGGCGG CATGGCG 17 (2) INFORMATION FOR SEQ ID NO:672: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(2) INFORMATION FOR SEQ ID NO:678:
 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: DNA (genomic)

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:678: TGGAGGGCGG	10
(2) INFORMATION FOR SEQ ID NO:679:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:679:  GGAGGGCGGC ATGGCGGGCA CAGGCTGGGC	30
(2) INFORMATION FOR SEQ ID NO:680:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:680:	30
GGAGGCGGC ATGGCGGGCA CAGGCTGGG	29
(2) INFORMATION FOR SEQ ID NO:681:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:681:	
GGAGGGCGGC ATGGCGGGCA CAGGCTGG	28
(2) INFORMATION FOR SEQ ID NO:682:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:682: GGAGGGCGGC ATGGCGGCA CAGGCTG	27
(2) INFORMATION FOR SEQ ID NO:683:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:683:	
GGAGGGCGGC ATGGCGGCA CAGGCT	26
(2) INFORMATION FOR SEQ ID NO:684:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:684: GGAGGGCGGC ATGGCGGCA CAGGC	25
(2) INFORMATION FOR SEQ ID NO:685:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:685:  GGAGGGCGGC ATGGCGGCA CAGG	24
OUACOUCOU ATGUCOUCA CAOC	24
(2) INFORMATION FOR SEQ ID NO:686:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:686:	
GGAGGGCGGC ATGGCGGGCA CAG	23
(2) INFORMATION FOR SEQ ID NO:687:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:687: GGAGGGCGGC ATGGCGGCA CA	22
(2) INFORMATION FOR SEQ ID NO:688:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:688:	
GGAGGGCGC ATGGCGGCA C	21
(2) INFORMATION FOR SEQ ID NO:689:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:689:	
GGAGGGCGGC ATGGCGGGCA	20
(2) INFORMATION FOR SEQ ID NO:690:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	

GGAG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:696: GGGCGGC ATG	13
(2)	INFORMATION FOR SEQ ID NO:697:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:697:  GGGCGGC AT	12
		12
(2)	INFORMATION FOR SEQ ID NO:698:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
GGAG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:698: GGGCGGC A	11
(2)	<pre>INFORMATION FOR SEQ ID NO:699:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 10 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear   (ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:699:</pre>	
GGAG	GGCCGC LL	10
	INFORMATION FOR SEQ ID NO:700:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:700:  GGCGGCA TGGCGGCCAC AGGCTGGGC	2.0
GAGG		29
(2)	INFORMATION FOR SEQ ID NO:701:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:701:  GGCGGCA TGGCGGGCAC AGGCTGGG	28
	INFORMATION FOR SEQ ID NO:702:	
(2)	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(2) INFORMATION FOR SEQ ID NO:708:
(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

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GAGGGCGCA TGGCGG

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:714: GAGGGCGGCA TGGCG	15
(2) INFORMATION FOR SEQ ID NO:715:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 14 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:715: GAGGGCGGCA TGGC	14
(2) INFORMATION FOR SEQ ID NO:716:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:716:	
GAGGGCGCA TGG	13
(2) INFORMATION FOR SEQ ID NO:717:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:717:	
GAGGGCGGCA TG	12
(2) INFORMATION FOR SEQ ID NO:718:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:718:	
GAGGGCGCA T	11
(2) INFORMATION FOR SEQ ID NO:719:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:719: GAGGGCGGCA	10
(2) INFORMATION FOR SEQ ID NO:720:	-0
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 28 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
(ii) MOLECULE TYPE: DNA (genomic)	

	JENCE DESCRIPTION: SEQ ID GCGGGCACA GGCTGGGC	NO:720:
(i) SEQU (A) (B) (C) (D) (ii) MOLH (xi) SEQU	JENCE CHARACTERISTICS:  LENGTH: 27 base pairs  TYPE: nucleic acid  STRANDEDNESS: single  TOPOLOGY: linear  ECULE TYPE: DNA (genomic)  JENCE DESCRIPTION: SEQ ID  GCGGGCCACA GGCTGGG	NO:721:
(i) SEQU (A) (B) (C) (D)	ION FOR SEQ ID NO:722:  JENCE CHARACTERISTICS:  LENGTH: 26 base pairs  TYPE: nucleic acid  STRANDEDNESS: single  TOPOLOGY: linear	
(xi) SEQ	ECULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID GCGGGCACA GGCTGG	NO:722:
(i) SEQU (A) (B) (C) (D) (ii) MOLH (xi) SEQU	ION FOR SEQ ID NO:723: JENCE CHARACTERISTICS: LENGTH: 25 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear ECULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID	NO:723:
(2) INFORMAT:  (i) SEQUE  (A)  (B)  (C)  (D)  (ii) MOLI  (xi) SEQUE	ION FOR SEQ ID NO:724: JENCE CHARACTERISTICS: LENGTH: 24 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear ECULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID	NO:724:
(2) INFORMAT:	GCGGGCACA GGCT  ION FOR SEQ ID NO:725: UENCE CHARACTERISTICS: LENGTH: 23 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear ECULE TYPE: DNA (genomic) UENCE DESCRIPTION: SEQ ID GCGGGCACA GGC	NO:725:
(i) SEQ (A (B (C (D	ION FOR SEQ ID NO:726: UENCE CHARACTERISTICS: LENGTH: 22 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear ECULE TYPE: DNA (genomic)	

(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:732:	
AGGGCGGCAT GGCGGG	16
(2) INFORMATION FOR SEQ ID NO:733:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:733:  AGGGCGGCAT GGCGG	· 15
(2) INFORMATION FOR SEQ ID NO:734:	
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:734:  AGGGCGGCAT GGCG	14
(2) INFORMATION FOR SEQ ID NO:735: (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 13 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:735: AGGGCGGCAT GGC	13
(2) INFORMATION FOR SEQ ID NO:736:	10
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:736:	
AGGGCGGCAT GG	12
(2) INFORMATION FOR SEQ ID NO:737:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:737:	
AGGGCGGCAT G	11
(2) INFORMATION FOR SEQ ID NO:738:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic)	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:744:	
GGGC	CGGCATG GCGGGCACAG GC	22
	INFORMATION FOR SEQ ID NO:745:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:745: CGGCATG GCGGGCACAG G	21
(2)	INFORMATION FOR SEQ ID NO:746: (i) SEQUENCE CHARACTERISTICS:	
202	<ul> <li>(A) LENGTH: 20 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:746:</li> </ul>	
	GGCATG GCGGGCACAG	20
(2)	<pre>INFORMATION FOR SEQ ID NO:747:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 19 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:747:</pre>	
GGGC	GGCATG GCGGGCACA	19
(2)	<pre>INFORMATION FOR SEQ ID NO:748:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 18 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:748:</pre>	
GGGC	GGCATG GCGGGCAC	18
(2)	<pre>INFORMATION FOR SEQ ID NO:749:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:749:</pre>	
GGGC	GGCATG GCGGGCA	17
(2)	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 16 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
	(ii) MOLECULE TYPE: DNA (genomic)	

#### BNSDOCID: <WO___9963938A2_I_>

(2) INFORMATION FOR SEQ ID NO:756: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:756: GGGCGGCATG	10
(2) INFORMATION FOR SEQ ID NO:757:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:757:  GGCGGCATGG CGGGCACAGG CTGGGC	26
(2) INFORMATION FOR SEQ ID NO:758:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 25 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:758: GGCGGCATGG CGGGCACAGG CTGGG	25
(2) INFORMATION FOR SEQ ID NO:759:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 24 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:759: GGCGGCATGG CGGGCACAGG CTGG	24
(2) INFORMATION FOR SEQ ID NO:760:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:760: GGCGGCATGG CGGGCACAGG CTG	23
(2) INFORMATION FOR SEQ ID NO:761:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 22 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:761: GGCCGGCATGG CGGGCACAGG CT	22
(2) INFORMATION FOR SEQ ID NO:762:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear(ii) MOLECULE TYPE: DNA (genomic)

### BNSDOCID: <WO___9963938A2_1_>

GGCG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:768: GGCATGG CGGGC	15
	INFORMATION FOR SEQ ID NO:769:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:769: GGCATGG CGGG	14
(2)	<pre>INFORMATION FOR SEQ ID NO:770:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 13 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:770: GGCATGG CGG</pre>	1.3
		13
	INFORMATION FOR SEQ ID NO:771:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:771:  GGCATGG CG	12
(2)	<pre>INFORMATION FOR SEQ ID NO:772:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:772: GGCATGG C</pre>	1.1
	<pre>INFORMATION FOR SEQ ID NO:773:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:773:</pre>	_
GGCC	GGCATGG	10
(2)	<pre>INFORMATION FOR SEQ ID NO:774:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	

GCGGCATGGC GGGCACAGGC TGGGC	25
(2) INFORMATION FOR SEQ ID NO:775:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:775:  GCGGCATGGC GGGCACAGGC TGGG	24
(2) INFORMATION FOR SEQ ID NO:776:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 23 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:776:</li> </ul>	
CCCCCC	23
(2) INFORMATION FOR SEQ ID NO:777:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:777:	
	22
(2) INFORMATION FOR SEQ ID NO:778:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:778:	
	21
(2) INFORMATION FOR SEQ ID NO:779:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:779:	
GCGGCATGGC GGGCACAGGC	20
(2) INFORMATION FOR SEQ ID NO:780:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	

BNSDOCID: <WO___9963938A2_I_>

GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:780: CCATGGC GGGCACAGG	19
	INFORMATION FOR SEQ ID NO:781:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:781: GCATGGC GGGCACAG	18
(2)	<pre>INFORMATION FOR SEQ ID NO:782:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:782:</pre>	
GCGG	CATGGC GGGCACA	17
	INFORMATION FOR SEQ ID NO:783:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:783: GCATGGC GGGCAC	16
	INFORMATION FOR SEQ ID NO:784:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:784: GCATGGC GGGCA	15
	INFORMATION FOR SEQ ID NO:785:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:785: GCATGGC GGGC	14
(2)	INFORMATION FOR SEQ ID NO:786:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	±-3

CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:792: ATGGCG GGCACAGGCT GG	22
	INFORMATION FOR SEQ ID NO:793:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:793:	
CGGC	CATGGCG GGCACAGGCT G	21
(2)	<pre>INFORMATION FOR SEQ ID NO:794:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:794: CATGGCG GGCACAGGCT	20
(2)	INFORMATION FOR SEQ ID NO:795: (i) SEQUENCE CHARACTERISTICS:	
	<ul> <li>(A) LENGTH: 19 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:795:</li> </ul>	
CGGC	CATGGCG GGCACAGGC	19
(2)	<pre>INFORMATION FOR SEQ ID NO:796:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:796:</pre>	
CGGC	CATGGCG GGCACAGG	18
(2)	INFORMATION FOR SEQ ID NO:797:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:797: CATGGCG GGCACAG	17
		- '
(2)	INFORMATION FOR SEQ ID NO:798:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	

CGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:798: CATGGCG GGCACA	16
(2)	<pre>INFORMATION FOR SEQ ID NO:799:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 15 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:799: CATGGCG GGCAC</pre>	15
(2)	<pre>INFORMATION FOR SEQ ID NO:800:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 14 base pairs      (B) TYPE: nucleic acid</pre>	
CGG	(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:800: CATGGCG GGCA	14
(2)	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 13 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:801: CATGGCG GGC	13
(2)	<pre>INFORMATION FOR SEQ ID NO:802:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 12 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:802:</pre>	
CGGC	CATGGCG GG	12
(2)	<pre>INFORMATION FOR SEQ ID NO:803:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:803: CATGGCG G	11
(2)	<pre>INFORMATION FOR SEQ ID NO:804:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 10 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear   (ii) MOLECULE TYPE: DNA (genomic)</pre>	

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CGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:804: CATGGCG	10
	INFORMATION FOR SEQ ID NO:805:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:805:	23
	<pre>INFORMATION FOR SEQ ID NO:806:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 22 base pairs      (B) TYPE: nucleic acid      (C) STRANDEDNESS: single      (D) TOPOLOGY: linear</pre>	
GGCA	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:806: TGGCGG GCACAGGCTG GG	22
	INFORMATION FOR SEQ ID NO:807:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:807:  ATGGCGG GCACAGGCTG G	21
(2)	INFORMATION FOR SEQ ID NO:808:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:808:	20
	INFORMATION FOR SEQ ID NO:809:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:809: ATGGCGG GCACAGGCT	19
(2)	<pre>INFORMATION FOR SEQ ID NO:810:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	

GGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:810: ATGGCGG GCACAGGC	18
	INFORMATION FOR SEQ ID NO:811:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:811: ATGGCGG GCACAGG	17
	INFORMATION FOR SEQ ID NO:812:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:812: ATGGCGG GCACAG	16
	INFORMATION FOR SEQ ID NO:813:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:813:	
GGCA	ATGGCGG GCACA	15
	INFORMATION FOR SEQ ID NO:814:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:814: ATGGCGG GCAC	14
	INFORMATION FOR SEQ ID NO:815:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:815:  ATGGCGG GCA	13
(2)	<pre>INFORMATION FOR SEQ ID NO:816:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 12 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear</pre>	- 0

GGCA	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:816: ATGGCGG GC	12
	INFORMATION FOR SEQ ID NO:817:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:817:  ATGGCGG G	11
(2)	INFORMATION FOR SEQ ID NO:818:	
	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 10 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
GGCA	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:818:	10
(2)	INFORMATION FOR SEQ ID NO:819:	
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:819:	22
	INFORMATION FOR SEQ ID NO:820:	22
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:820: FGGCGGG CACAGGCTGG G	21
	INFORMATION FOR SEQ ID NO:821:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:821:	20
	TGGCGGG CACAGGCTGG	20
(2)	INFORMATION FOR SEQ ID NO:822:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

(2) INFORMATION FOR SEQ ID NO:834: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

## TGGCGGCAC AGGCTGG (2) INFORMATION FOR SEQ ID NO:858: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

## (2) INFORMATION FOR SEQ ID NO:864: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 10 base pairs (B) TYPE: nucleic acid

(C) STRANDEDNESS: single (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:864: TGGCGGGCAC	10
(2) INFORMATION FOR SEQ ID NO:865:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS:.single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:865: GGCGGGCACA GGCTGGGC	18
(2) INFORMATION FOR SEQ ID NO:866:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:866: GGCGGGCACA GGCTGGG	17
(2) INFORMATION FOR SEQ ID NO:867:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:867: GGCGGGCACA GGCTGG	16
(2) INFORMATION FOR SEQ ID NO:868:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:868:  GGCGGGCACA GGCTG	15
(2) INFORMATION FOR SEQ ID NO:869:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:869: GGCGGGCACA GGCT	14
(2) INFORMATION FOR SEQ ID NO:870:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

GCGGGCACAG GCTGGG

(2) INFORMATION FOR SEQ ID NO:876: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:876: GGCACAG GCTGG	15
	INFORMATION FOR SEQ ID NO:877:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:877:	
GCGC	GGCACAG GCTG	14
(2)	<pre>INFORMATION FOR SEQ ID NO:878:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 13 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CCC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:878:	
GCGC	GGCACAG GCT .	13
(2)	<pre>INFORMATION FOR SEQ ID NO:879:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 12 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:879:	12
	INFORMATION FOR SEQ ID NO:880:	12
	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 11 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:880:</li> </ul>	
GCG	GGCACAG G	11
(2)	INFORMATION FOR SEQ ID NO:881:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:881:</pre>	
GCG	GGCACAG	10
(2)	INFORMATION FOR SEQ ID NO:882:	
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:882: CGGGCACAGG CTGGGC	16
(2) INFORMATION FOR SEQ ID NO:883:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 15 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:883: CGGGCACAGG CTGGG	15
(2) INFORMATION FOR SEQ ID NO:884:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:884:  CGGGCACAGG CTGG	14
(2) INFORMATION FOR SEQ ID NO:885:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:885:  CGGGCACAGG CTG	14
(2) INFORMATION FOR SEQ ID NO:886:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:886:  CGGGCACAGG CT	13
(2) INFORMATION FOR SEQ ID NO:887:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:887:  CGGGCACAGG C	
(2) INFORMATION FOR SEQ ID NO:888:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	11

CGGG	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:888: GCACAGG	10
(2)	INFORMATION FOR SEQ ID NO:889:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:889: CACAGGC TGGGC	15
(2)	<pre>INFORMATION FOR SEQ ID NO:890:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 14 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GGGC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:890: CACAGGC TGGG	14
	INFORMATION FOR SEQ ID NO:891:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:891:	
	CACAGGC TGG	13
	INFORMATION FOR SEQ ID NO:892:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:892:	
(2)	INFORMATION FOR SEC ID NO. 223.	12
	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 11 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:893:</li> </ul>	
	CACAGGC T INFORMATION FOR SEQ ID NO:894:	13
(4)	<ul><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 10 base pairs</li><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li><li>(D) TOPOLOGY: linear</li></ul>	
	(ii) MOLECULE TYPE: DNA (genomic)	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:894: GGGCACAGGC	10
(2) INFORMATION FOR SEQ ID NO:895:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:895: GGCACAGGCT GGGC	14
(2) INFORMATION FOR SEQ ID NO:896:	
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 13 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> </ul>	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:896: GGCACAGGCT GGG	13
	13
(2) INFORMATION FOR SEQ ID NO:897:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:897: GGCACAGGCT GG	12
(2) INFORMATION FOR SEQ ID NO:898:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:898: GGCACAGGCT G	11
(2) INFORMATION FOR SEQ ID NO:899:	11
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:899:  GGCACAGGCT	
	10
(2) INFORMATION FOR SEQ ID NO:900:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 13 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear	

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GCAC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:900: CAGGCTG GGC	13
	INFORMATION FOR SEQ ID NO:901:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:901: CAGGCTG GG	12
(2)	<pre>INFORMATION FOR SEQ ID NO:902: (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 11 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCAC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:902: CAGGCTG G	11
	<pre>INFORMATION FOR SEQ ID NO:903:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 10 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear   (ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:903:</pre>	
	CAGGCTG	10
	INFORMATION FOR SEQ ID NO:904:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:904:	
	AGGCTGG GC	12
(2)	<pre>INFORMATION FOR SEQ ID NO:905:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:905:</pre>	
CACA	AGGCTGG G	11
(2)	<pre>INFORMATION FOR SEQ ID NO:906:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
	(II) HOLDCODE IIIE. DIA (GEHOMIC)	

(x1) SEQUENCE DESCRIPTION: SEQ ID NO: 906: CACAGGCTGG	10
(2) INFORMATION FOR SEQ ID NO:907:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:907:	
ACAGGCTGGG C	11
(2) INFORMATION FOR SEQ ID NO:908:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:908: ACAGGCTGGG	
	10
(2) INFORMATION FOR SEQ ID NO:909:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:909:	<del></del>
CAGGCTGGGC	10
(2) INFORMATION FOR SEQ ID NO:910:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 51 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:910:	
GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C  (2) INFORMATION FOR SEQ ID NO:911:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 50 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:911:	51
GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGGC	50
(2) INFORMATION FOR SEQ ID NO:912:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 49 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:912:	

CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC	49
(2) INFORMATION FOR SEQ ID NO:913:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 48 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:913:  GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGGGC	48
(2) INFORMATION FOR SEQ ID NO:914:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 47 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:914:  GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG GCTGGGC	47
(2) INFORMATION FOR SEQ ID NO:915:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 46 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:915:  CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGGGC	46
(2) INFORMATION FOR SEQ ID NO:916:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 45 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:916:  CTGGAAAGCT GAGATGGAGG GCGGCATGGC GGGCACAGGC TGGGC	45
(2) INFORMATION FOR SEQ ID NO:917:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 44 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:917: TGGAAAGCTG AGATGGAGGG CGGCATGGCG GGCACAGGCT GGGC	4 4
(2) INFORMATION FOR SEQ ID NO:918:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:918:	

GGAAAGCTGA GATGGAGGCC GGCATGGCGG GCACAGGCTG GGC	43
(2) INFORMATION FOR SEQ ID NO:919:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 42 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:919: GAAAGCTGAG ATGGAGGGCG GCATGGCGGG CACAGGCTGG GC	42
(2) INFORMATION FOR SEQ ID NO:920:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 41 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:920: AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C	41
(2) INFORMATION FOR SEQ ID NO:921:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 40 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:921:  AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGGC	40
(2) INFORMATION FOR SEQ ID NO:922:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 39 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:922: AGCTGAGATG GAGGGCGCA TGGCGGGCAC AGGCTGGGC	39
(2) INFORMATION FOR SEQ ID NO:923:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:923:	
GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGGGC  (2) INFORMATION FOR SEQ ID NO:924:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	38
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:924: CTGAGATGGA GGGCGCATG GCGGGCACAG GCTGGGC	37

(2)	INFORMATION FOR SEQ ID NO:925:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 36 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:925:	
TGAG	GATGGAG GGCGGCATGG CGGGCACAGG CTGGGC	36
(2)	INFORMATION FOR SEQ ID NO: 926:	
, ,	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 35 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:926:	
CNCN	ATGGAGG GCGCATGCC GGGCACAGGC TGGGC	35
GAGE	AIGGAGG GCGGCAIGGC GGGCACAGGC IGGGC	35
121	INFORMATION FOR SEQ ID NO:927:	
(2)		
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 34 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:927:	
AGAI	rggaggg cggcatggcg ggcacaggct gggc	34
(2)		
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 33 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:928:	
GATO	GGAGGGC GGCATGGCGG GCACAGGCTG GGC	33
(2)	INFORMATION FOR SEQ ID NO:929:	
, ,	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:929:	
ATGO	GAGGGCG GCATGGCGGG CACAGGCTGG GC	32
		52
(2)	INFORMATION FOR SEQ ID NO:930:	
_/	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic)	
TCC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:930:	

	INFORMATION FOR SEQ ID NO:931:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:931:  GGGCGGC ATGGCGGCCA CAGGCTGGGC	30
		30
	INFORMATION FOR SEQ ID NO:932:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:932: GGCGGCA TGGCGGCCAC AGGCTGGCC	29
(2)	INFORMATION FOR SEQ ID NO:933: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
<b>N</b> GG0	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:933: GCGGCAT-GGCGGGCACA-GGCTGGGC	20
		2-8-
	INFORMATION FOR SEQ ID NO:934:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:934:  CGGCATG GCGGGCACAG GCTGGGC	27
	INFORMATION FOR SEQ ID NO:935:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:935: GGCATGG CGGGCACAGG CTGGGC	26
(2)	<pre>INFORMATION FOR SEQ ID NO:936:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 25 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:936:</pre>	
GCGG	GCATGGC GGGCACAGGC TGGGC	25

(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:937:  CGGCATGGCG GGCACAGGCT GGGC	24
(2) INFORMATION FOR SEQ ID NO:938:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:938: GGCATGGCGG GCACAGGCTG GGC	23
(2) INFORMATION FOR SEQ ID NO:939:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:939:  GCATGGCGGG CACAGGCTGG GC	22
(2) INFORMATION FOR SEQ ID NO:940:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:940:  CATGGCGGGC ACAGGCTGGG C	21
(2) INFORMATION FOR SEQ ID NO:941:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:941: ATGGCGGGCA CAGGCTGGGC	20
(2) INFORMATION FOR SEQ ID NO:942:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:942: TGGCGGGCAC AGGCTGGGC	19

	INFORMATION FOR SEQ ID NO:943:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:943: GGGCACA GGCTGGGC	18
(2)	<pre>INFORMATION FOR SEQ ID NO:944:   (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:944:</pre>	
GCG	GGCACAG GCTGGGC	17
(2)	<pre>INFORMATION FOR SEQ ID NO:945:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 16 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
egge	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:945: GCACAGG_CTGGGC	16
	INFORMATION FOR SEQ ID NO:946:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:946: CACAGGC TGGGC	15
	INFORMATION FOR SEQ ID NO:947:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:947:  ACAGGCT GGGC	14
	INFORMATION FOR SEQ ID NO:948:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:948:	
121 1/1/	PAGGCTG GGC	

	INFORMATION FOR SEQ ID NO:949:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:949: AGGCTGG GC	12
(2)	<pre>INFORMATION FOR SEQ ID NO:950:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 11 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:950:</pre>	
ACAG	GGCTGGG C	11
(2)	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 10 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:951:	
CAGG	SCTGGGC	10
	<pre>INFORMATION FOR SEQ ID NO:952:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 9 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:952: CTGGGC</pre>	9
(2)	<pre>INFORMATION FOR SEQ ID NO:953:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 23 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single             (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:953: TCC TTC CTT TGT CTC TCT TC</pre>	23
(2)	INFORMATION FOR SEQ ID NO:954:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:954:	1 5
GCT	CCC GGC TGC CTG	15

(2) INFORMATION FOR SEQ ID NO:957:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:957:  TGG—TGC—CGT—TGG—CTG—CCC  (2) INFORMATION FOR SEQ ID NO:958:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:958:  CTT CTG CGG GTC GCC GG  (2) INFORMATION FOR SEQ ID NO:959:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (XI) SEQUENCE DESCRIPTION: SEQ ID NO:959:  (II) SEQUENCE CHARACTERISTICS:  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (XI) SEQUENCE DESCRIPTION: SEQ ID NO:959:	INFORMATION FOR SEQ ID NO:955:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:955:  GGC CGT GCG GCT CTG TCG CTC CCG GT	29
(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:957:  TGC—TGC—CGT—TGC_CCC  (2) INFORMATION FOR SEQ ID NO:958: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 17 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:958:  CTT CTG CGG GTC GCC GG  (2) INFORMATION FOR SEQ ID NO:959: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:959:  TGC TGG GCT TGT GGC  (2) INFORMATION FOR SEQ ID NO:960: (i) SEQUENCE DESCRIPTION: SEQ ID NO:959: TGC TGG GCT TGT GGC  (2) INFORMATION FOR SEQ ID NO:960: (i) SEQUENCE DESCRIPTION: SEQ ID NO:959: TGC TGG GCT TGT GGC  (2) INFORMATION FOR SEQ ID NO:960: (i) SEQUENCE DESCRIPTION: SEQ ID NO:959: TGC TGG GCT TGT GGC  (2) INFORMATION FOR SEQ ID NO:960: (i) SEQUENCE DESCRIPTION: SEQ ID NO:960:	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:956:	20
(i) SEQUENCE CHARACTERISTICS:	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 18 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:957:</li> </ul>	18
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:959:  TGC TGG GCT TGT GGC  (2) INFORMATION FOR SEQ ID NO:960:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:960:	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 17 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:958:</li> </ul>	17
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 15 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:960:</li> </ul>	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 15 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:959:</li> </ul>	15
	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 15 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:960:</li> </ul>	

	INFORMATION FOR SEQ ID NO:961:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGT CCC TCC GT	NO:961:	14
(2)	INFORMATION FOR SEQ ID NO:962:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGC TCC TCT GC	NO:962:	14
(2)	INFORMATION FOR SEQ ID NO:963:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  TGG TCC TGG GGC TGC	NO:963:	18
(2)	INFORMATION FOR SEQ ID NO:964:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID TCT CCT CTC CTT	NO:964:	15
	INFORMATION FOR SEQ ID NO:965:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  TTT TCT TTT CTG GGC CTC	NO: 965:	21
(2)	INFORMATION FOR SEQ ID NO:966:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID	NO: 966:	

TGT	GGT CTG TTT TCT G	19
	INFORMATION FOR SEQ ID NO:967:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:967:  CTG CTG GGG CGC TCT CC	20
(2)	<pre>INFORMATION FOR SEQ ID NO:968:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 18 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:968:</pre>	
GCC	GCC CGC CTG GCT CCC-3=	18
(2)	<pre>INFORMATION FOR SEQ ID NO:969:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 21 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    _(xi)_SEQUENCE DESCRIPTION: SEQ ID NO:969: GCC CBT GBT GGG CBT GCC</pre>	21
(2)	INCODMANTON FOR ORD ID NO 070	
(2)	INFORMATION FOR SEQ ID NO:970:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:970:	
GTG	GTT CTT GCC CTC CTT TGG CTG	24
	<pre>INFORMATION FOR SEQ ID NO:971:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:971: TGC CCG CTC CCC GGC</pre>	18
(2)	INFORMATION FOR SEQ ID NO:972:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	

CTC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:972: CTG GCG GGT GGC CGT TG	20
(2)	<pre>INFORMATION FOR SEQ ID NO:973:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single             (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:973: CCG TGT TCC CCT GGG</pre>	18
(2)	<pre>INFORMATION FOR SEQ ID NO:974: (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
GCC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:974: TGG GGC TCC CTT CTC TC	20
	<pre>INFORMATION FOR SEQ ID NO:975:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 19 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single             (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:975: CTT CTT GCT GGG CCT C</pre>	19
(2)	<pre>INFORMATION FOR SEQ ID NO:976:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 25 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:976: TGC TGC TGG TGC TGT GGC CCC C</pre>	25
(2)	INFORMATION FOR SEQ ID NO:977:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:978: CACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC	43
(2)	<pre>INFORMATION FOR SEQ ID NO:978: (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 43 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear</pre>	

GTB	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:978: CBCCGBGGBGCCCBTGBTGGGCBTGCCBCBGBCGBCBGGC	43
(2)	<ul> <li>(i) SEQUENCE CHARACTERISTICS: <ul> <li>(A) LENGTH: 29 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul> </li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:979:</li> </ul>	
	GCC GTG CCG CGT CTT GGT GGC GGC GG	29
(2)	<pre>INFORMATION FOR SEQ ID NO:980:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 30 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:980:</pre>	
GTT	CGC GCC CGC GCG GCC CTC CGG TCC	30
(2)	<pre>INFORMATION FOR SEQ ID NO:981:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 35 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:981: GCC CGC GCG CCC GCC CGT CTC GGG CTG GGC GG</pre>	35
(2)	<pre>INFORMATION FOR SEQ ID NO:982:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:982:</pre>	
	GTC GGG GCC CCC CGC GGC C	22
(2) GCC	<pre>INFORMATION FOR SEQ ID NO:983:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 29 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:983: TCG GGG CTG GGG CGC TGG TGG CCG GG</pre>	29
(2)	INFORMATION FOR SEQ ID NO:984: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 24 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single	

CCG	(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:984: CGC CTC CGC CTG CCG CTT CTG	24
(2)	INFORMATION FOR SEQ ID NO:985:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:985:	
GCT	GGG CCC CGG GCG CCC CCT	21
(2)	<pre>INFORMATION FOR SEQ ID NO:986:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 23 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)</pre>	
CCC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:986: CTC TTG CTC GGG TCC CCG TG	23
		23
(2)	INFORMATION FOR SEQ ID NO:987:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 48 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:987:	
ACAC	GCGCGTCCTGTGTCTCCAGCAGCATGGCCGGGCCAGCTGGGCCCC	48
(2)	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 48 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
	<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:988:</pre>	
всво	GCGCGTCCTGTGTCTCCBGCBGCBTGGCCGGGCCBGCTGGGCCCC	48
(2)	<pre>INFORMATION FOR SEQ ID NO:989:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: _ base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear</pre>	
	<pre>(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:989:</pre>	
ACA	GAG CAT GCT GTT GGG CAT CTT GCC TTC CCA GGG	39
(2)	<pre>INFORMATION FOR SEQ ID NO:990:   (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 39 base pairs      (B) TYPE: nucleic acid</pre>	

всв	(C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:990: GBG CB TGC TGT TGG GCB TCT TGC CTT CCC BGG G	39
(2) CCC	<pre>INFORMATION FOR SEQ ID NO:991:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 18 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear   (ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:991: TTT TCT GGT GGG GTG</pre>	18
	INFORMATION FOR SEQ ID NO:992:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:992:  CTG TTG TTG GGC	15
	INFORMATION FOR SEQ ID NO:993:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:993:  CTT CTG TTC CC	14
(2) CCC	INFORMATION FOR SEQ ID NO:994:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:994: TTT TCT GGT GGG GTG	18
	INFORMATION FOR SEQ ID NO:995:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:995:  CTG TTG TTG GGC	15
(2)	INFORMATION FOR SEQ ID NO:996: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 14 base pairs	

TTT	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO	D:996:
(2)	INFORMATION FOR SEQ ID NO:997:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
CTC	(xi) SEQUENCE DESCRIPTION: SEQ ID NO GTC GCC GTC GCC GGC GGG	D: 997: 21
(2)	INFORMATION FOR SEQ ID NO:998:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO	
GGG	TGG TGC TAT TGT CGG GC	20
	INFORMATION FOR SEQ ID NO:999:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO	D: 999:
GGC	CCA GGG CCA GCC	15
	INFORMATION FOR SEQ ID NO:1000:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO	
	CGG GCC AGC CGG GCC CGG	21
	INFORMATION FOR SEQ ID NO:1001:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO GGA GGG CGG CAT GGC GGG	O:1001:
(2)	INFORMATION FOR SEQ ID NO:1002: (i) SEQUENCE CHARACTERISTICS:	

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GTA	(A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID GGT GGC GGG CAA GGC GGG	NO:1002:	2:
	INFORMATION FOR SEQ ID NO:1003:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGA GGC GGG CAT GGC GGG	NO:1003:	23
	INFORMATION FOR SEQ ID NO:1004:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGA GGG CGG CAT GGC GGG	NO:1004:	21
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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

1) International Patent Classification ⁶ : A61K 48/00, C07H 21/04, 21/00, C12N 5/00, 15/63, 15/79, 15/09	A3	(11) International Publication Number: WO 99/63938 (43) International Publication Date: 16 December 1999 (16.12.99)
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60/088,501 8 June 1998 (08.06.98) 09/093,972 9 June 1998 (09.06.98) 60/088,657 9 June 1998 (09.06.98)  1) Applicant (for all designated States except US): EPI PHARMACEUTICALS, INC. [US/US]; 2005 Eas 130), Cranbury, NJ 08512 (US).  2) Inventors; and 5) Inventors/Applicants (for US only): NYCE, Jon [US/US]; 59 Sayre Drive, Princeton, NJ 08540 (US/US); 59 Sayre Drive, Princeton, NJ 08540 (US/US); 2419 Sedgefield Drive, Cl NC 27514 (US).  4) Agent: AMZEL, Viviana; Arter & Hadden LLP, S Citicorp Plaza, 725 S. Figueroa Street, Los An 90017 (US).	athan, VIS). HIL napel H	Before the expiration of the time limit for amending the claim and to be republished in the event of the receipt of amendments.  (88) Date of publication of the international search report:  27 January 2000 (27.01.00

(54) Title: COMPOSITION AND METHOD FOR PREVENTION AND TREATMENT OF CARDIOPULMONARY AND RENAL FAILURE OR DAMAGE ASSOCIATED WITH ISCHEMIA, ENDOTOXIN RELEASE, ARDS OR BROUGHT ABOUT BY ADMINISTRATION OF CERTAIN DRUGS

#### (57) Abstract

A pharmaceutical composition comprises an agent such as an adenosine A2a agonist agent and/or nucleic acid comprising an oligonucleotide(oligo) that is anti-sense to an adenosine A1, A2a, A2b or A3 receptor gene, mRNA, flanking regions or regions bridging the intro/exon borders, which oligos are effective to prevent, alleviate or inhibit adenosine-mediated cardiac, pulmonary and/or renal functional difficulties, damage or failure, such as those observed in diseases and conditions such as ARDS, hypoxia, etc. or associated with the administration of therapeutic and diagnostic agents such as adenosine cysplatin, metal ion-containing agents, etc., mixtures thereof, and optionally a surfactant, a carrier and other therapeutic and diagnostic agents and other formulation components. The composition is provided in the form of various formulations that are, for example, effective for preventing or alleviating bronchoconstriction, allergy and/or inflammation associated with ARDS, RDS, etc., deleterious side effects observed upon treatment of SVT patients, upon administration of cardiac stress tests or imaging tests, etc.

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## INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/12775

A. CLASSIFICATION OF SUE IPC(6) :A61K 48/00; C07H 21/ US CL :536/23.1, 23.2, 24.5, 2 According to International Patent Cl	04, 21/00; C12N 5/00, 15/6 4.3; 435/91.1, 375, 6; 514/	/44				
B. FIELDS SEARCHED						
Minimum documentation searched (	classification system followe	d by classification symbols)				
U.S. : 536/23.1, 23.2, 24.5, 24	1.3; 435/91.1, 375, 6; 514/4	<del></del>				
Documentation searched other than m	inimum documentation to the	extent that such documents are included	in the fields searched			
USPTO NPL, Proquest-Direct						
Electronic data base consulted durin	g the international search (na	ame of data base and, where practicable	e, search terms used)			
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C. DOCUMENTS CONSIDERI	ED TO BE RELEVANT					
Category* Citation of docume	nt, with indication, where ap	ppropriate, of the relevant passages	Relevant to claim No.			
X WO 96/40266 A1 1996, page 7, lin		UNIVERSITY) 19 December	1-79			
X WO 98/23294 A 1998, page 1, lin		NA UNIVERSITY) 04 June	1-79			
Further documents are listed	in the continuation of Box C	See patent family annex.				
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International application No. PCT/US99/12775

APS, STN-Caplus, Inpadoc, Dialog-Medline, Biotech-Biobus cluster search terms: antisense, ribozyme, aptamer, triplex, adenosine receptor, cardiopulmonary and renal failure or disease or disorder, endotoxin release, acute respiratory distress syndrome or ARDS, ischemia								

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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application (22) International Filing Date:		S99/127 (08.06.9	(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT,
09/093,972 9 60/088,657 9  (71) Applicant (for all designate PHARMACEUTICALS 130), Cranbury, NJ 085  (72) Inventors; and (75) Inventors/Applicants (for [US/US]; 59 Sayre Driv Jeffrey, L. [US/US]; 20 NC 27514 (US).  (74) Agent: AMZEL, Viviana;	S, INC. [US/UŚ]; 2005 East 12 (US).  US only): NYCE, Jon ve, Princeton, NJ 08540 (U 419 Sedgefield Drive, C	IGENES st Park (Fathan, Vols). HILL hapel Hi	t. 27 January 2000 (27.01.00)

(54) Title: COMPOSITION AND METHOD FOR PREVENTION AND TREATMENT OF CARDIOPULMONARY AND RENAL FAILURE OR DAMAGE ASSOCIATED WITH ISCHEMIA, ENDOTOXIN RELEASE, ARDS OR BROUGHT ABOUT BY ADMINISTRATION OF CERTAIN DRUGS

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A pharmaceutical composition comprises an agent such as an adenosine A2a agonist agent and/or nucleic acid comprising an oligonucleotide(oligo) that is anti-sense to an adenosine A1, A2a, A2b or A3 receptor gene, mRNA, flanking regions or regions bridging the intro/exon borders, which oligos are effective to prevent, alleviate or inhibit adenosine-mediated cardiac, pulmonary and/or renal functional difficulties, damage or failure, such as those observed in diseases and conditions such as ARDS, hypoxia, etc. or associated with the administration of therapeutic and diagnostic agents such as adenosine cysplatin, metal ion-containing agents, etc., mixtures thereof, and optionally a surfactant, a carrier and other therapeutic and diagnostic agents and other formulation components. The composition is provided in the form of various formulations that are, for example, effective for preventing or alleviating bronchoconstriction, allergy and/or inflammation associated with ARDS, RDS, etc., deleterious side effects observed upon treatment of SVT patients, upon administration of cardiac stress tests or imaging tests, etc.

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COMPOSITION & METHOD FOR PREVENTION & TREATMENT OF CARDIOPULMONARY & RENAL FAILURE OR DAMAGE ASSOCIATED WITH ISCHEMIA, ENDOTOXIN RELEASE, ARDS OR BROUGHT ABOUT BY ADMINISTRATION OF CERTAIN DRUGS

#### **BACKGROUND OF THE INVENTION**

#### Field of the Invention

This invention relates to a composition, formulations and method for prevention and therapy of cardiac, cardiopulmonary and renal damage or failure seen in certain diseases or conditions associated with ischemia and/or endotoxin release, acute respiratory distress syndrome (ARDS), or brought about by administration of certain drugs such as cancer chemotherapeutic agents, glycerol, radiocontrast media, and adenosine which is administered, for example, in stress tests and the treatment of supraventricular tachycardia (SVT).

#### Description of the Background

Adenosine, a natural nucleoside, may constitute an important natural mediator of many of diseases, including asthma, and the like. The inhalation of adenosine by asthmatics, but not by normal subjects, causes broncho-constriction. Theophylline, a xanthine, may be useful in reversing this asthmatic effect. Other experimental data suggest the possibility that adenosine receptors may also be involved in allergic and inflammatory responses. It has been postulated that the modulation of signal transduction at the surface of inflammatory cells influences acute inflammation. Adenosine is said to inhibit the production of super-oxide by stimulated neutrophils. Moreover, the treatment of experimental allergic uveitis produced a marked reduction in inflammation. Adenosine may attenuate this behavior by reducing the hyperactivity of the central dopaminergic system.

Adenosine plays a unique role in the body as a regulator of cellular metabolism. It can raise the cellular level of AMP, ADP and ATP which are the energy intermediates of the cell. Adenosine can stimulate or down regulate the activity of adenylate cyclase and hence regulate cAMP levels. CAMP, in turn, plays a role in neurotransmitter release, cellular division and hormone release. Adenosine's major role appears to be to act as a protective injury autocoid. In any condition in which ischemia, low oxygen tension or trauma occurs adenosine appears to play a role. Defects in synthesis, release, action and/or degradation of adenosine have been postulated to contribute to the over activity of the brain excitatory amino acid neurotransmitters, and hence various pathological states. Recent evidence suggests that adenosine may also play a protective role in stroke, CNS trauma, epilepsy, ischemic heart disease, coronary by-pass, radiation exposure and inflammation.

Overall, adenosine appears to regulate cellular metabolism through ATP, to act as a carrier for methionine, to decrease cellular oxygen demand and to protect cells from ischemic injury. Adenosine is a tissue hormone or inter-cellular messenger that is released when cells are subject to ischemia, hypoxia, cellular stress, and increased workload, and or when the demand for ATP exceeds its supply. Adenosine is a purine and its formation is directly linked to ATP catabolism. It appears to modulate an array of physiological processes including vascular tone, hormone action, neural function, platelet aggregation and lymphocyte differentiation. It also may play a role in DNA formation, ATP biosynthesis and general intermediary metabolism. It is suggested that it regulates the formation of cAMP in the brain and in a variety of peripheral tissues. Adenosine is also said to participate in the auto-regulation of blood flow in the heart, brain, skeletal muscle, adipose tissue and kidney. In the kidney, for example, it may act as a

vasoconstrictor, but as a vasodilator in each of the other vascular beds. Adenosine is said to antagonize the catabolic effects of hormones and promote the action of the anabolic hormone insulin. In addition, adenosine may also act to attenuate the release of neurotransmitters in both the central and peripheral nervous systems, inhibit the secretion of insulin and prevent platelet aggregation. Adenosine has been said to modulate the function of T lymphocytes by a mechanism which involves the regulation of protein synthesis. Adenosine regulates cAMP formation through two receptors  $A_1$  and  $A_2$ . Via  $A_1$  receptors, adenosine reduces adenylate cyclase activity, while it stimulates adenylate cyclase at  $A_2$  receptors. The adenosine  $A_1$  receptors are more sensitive to adenosine than the  $A_2$  receptors. The CNS effects of adenosine are generally believed to be  $A_1$ -receptor mediated, where as the peripheral effects such as hypotension, bradycardia, are said to be  $A_2$  receptor mediated.

Adenosine is said to modulate adenylate cyclase activity as well as nerve cell firing and the release of neurotransmitters such as aspartate, glutamate, GABA and serotonin. It has sedative and anticonvulsive properties and is said to inhibit both spontaneous and evoked nerve firing. Its action is antagonized by caffeine and theophylline. Adenosine's action is mediated through cell surface receptors called  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  and  $A_3$ , and it acts as a purinergic inhibitory neuro or cellular transmitter. Adenosine also has been implicated in anxiety, analgesia, sleep and depression, in modifying CNS alertness, acting as neuro-modulator, which actions are terminated by cellular uptake or deamination. It also has been said to potentiate the effects of histamine, reduce neuronal excitability, and to exert the majority of its central effects pre-synaptically by inhibition of calcium-dependent neurotransmitter release.

It has been also suggested than the production and release of adenosine is closely linked to energy balance. During ischemia, adenosine levels accumulate and ATP is rapidly depleted. It appears to be released at the site of trauma or when the cellular oxygen supply is reduced by hypoxia or ischemia and, thus, dampens cellular activity and increases blood flow via vascular dilation. A localized increase of adenosine at traumatic foci plays an important homeostatic role by down-regulating physiological function and, thereby, conserving ATP. In almost every organ ischemia induces an elevation of adenosine levels, which results in a slowing of that organ's function, a process which is postulated to be mediated by adenosine receptors. In recognition of this, adenosine has been termed a "retaliatory metabolite" and an endogenous neuro-protective agent. Adenosine, therefore, appears to play overall a homeostatic role throughout the body or, in a sense, to generate recovery time for traumatized tissue.

Adenosine has been implicated in the regulation of coronary blood flow and said to have negative chromotropic and inotrophic effects on heart contractibility. These effects may be mediated directly via adenosine receptors, or indirectly by either inhibition of the release of other neurotransmitters or by antagonism of the myocardial action of noradrenalin. Adenosine injections have been used for the treatment of supraventricular tachycardia (SVT). During hypoxia, ischemia or reactive hyperaemia, adenosine appears to be freely released and, through its action reduce cellular hypoxic stress by slowing cellular metabolism. Thus, it appears to act as an anti-injury autocoid. It is believed that both morbidity and mortality from acute coronary artery occlusion may be reduced if local myocardial adenosine concentration is augmented. Adenosine is said to increase collateral coronary circulation and even inhibit the generation of superoxide anions by granulocytes, thus reducing vascular endothelial damage. Another effect of adenosine appears to be to block granulocyte activation, and thereby reduce capillary plugging and the "no-reflow" phenomenon which contributes to post-stroke neuro-degeneration.

Adenosine and a majority of adenosine mononucleotides have been said to also possess radioprotective activity. This protective activity is thought to occur through A₁ receptors. Internal kidney vasoconstriction, however, has been observed upon the administration of radiocontrast agents for imaging purposes. Adenosine, calcium and ischemia have been postulated to have a role in this radiocontrast agent-induced intra-renal vasoconstriction. Ischemia or oxygen derivation in many instances are said to produce kidney damage. Certain cancer chemotherapeutic agents, such as cisplatin and methotrexate, as well as glycerol and the administration of metal ions such as thallium (Th), lead (Pb) and cadmium (Cd) have also been associated with kidney damage, which may become extensive upon the release of endotoxins, and even culminate in sepsis. Known adenosine receptor antagonists have been said to attenuate the thus produced renal damage. Adenosine, thus, may have a role as a natural mediator of intra-renal vasocontriction. In particular, the kidney has a significant number of adenosine receptors, adenosine's effect on the kidneys could be mediated primarily through the stimulation of adenosine receptors.

One of the characteristics of hyper-responsive subjects in particular is the over-expression of the adenosine A₁ receptor. When activated by adenosine, whose levels are induced, for example, by ischemia or by certain agents such as glycerol, endotoxin, chemotherapeutic agents such as cisplatin and methotrexate, and by radiocontrast media, the adenosine A₁ receptor may cause life threatening, even fatal, renal damage. Adenosine receptor antagonists, such as theophylline, 8-cyclopentyl-1, 3-dipropylxanthine (DPCPX), are known to counter adenosine-mediated bronchoconstriction in asthmatics. Theophylline has been also employed to prevent a reduction in the glomerular filtration rate observed upon administration of a radiocontrast medium. The therapeutic potential, however, of currently available adenosine A₁ receptor-specific antagonists is drastically limited by their toxicity. Theophylline, for example, frequently results in significant toxicity because of its narrow therapeutic dose range. The availability of an alternative strategy to prevent and treat the adenosine associated renal dysfunction, damage and failure observed in patients with hypoxia or ischemia, and upon the administration of certain drugs, particularly in hyperresponsive individuals, would clearly be of extreme prophylactic and therapeutic value.

Adenosine A₁-mediated diseases and conditions, such as asthma, allergic rhinitis, and Acute Respiratory Distress Syndrome (ARDS), including in pregnant mothers, and RDS in premature born infants, among others, are common diseases in industrialized countries, and in the United States alone account for extremely high health care costs. These diseases or conditions have recently been increasing at an alarming rate, both in terms of prevalence, morbidity and mortality. In spite of this, their underlying causes still remain poorly understood. Acute Respiratory Distress Syndrome (ARDS) is also known in the medical literature as stiff lung, shock lung, pump lung and congestive atelectasis, and its incidence is 1 out of 100,000 people. ARDS is believed to be caused by a failure of the respiratory system characterized by fluid accumulation within the lung which, in turn, causes the lung to stiffen. The condition is triggered by a variety of processes that injure the lungs. In general ARDS occurs as a medical emergency. It may be caused by a variety of conditions that directly or indirectly cause the blood vessels to "leak" fluid into the lungs. In ARDS, the ability of the lungs to expand is severely decreased and damage to the air sacs and lining (endothelium) of the lung is extensive. The concentration of oxygen in the blood remains very low in spite of high concentrations of supplemental oxygen which are

generally administered to a patient. Among the systemic causes of lung injury are trauma, head injury, shock, sepsis, multiple blood transfusions and medications. Pulmonary causes include pulmonary embolism, severe pneumonia, smoke inhalation, radiation, high altitude, near drowning, and more. ARDS symptoms usually develop within 24 to 48 hours of the occurrence of an injury or illness. It is believed that cigarette smoking may be a risk factor.

Among the most common symptoms of ARDS are labored, rapid breathing, nasal flaring, cyanosis blue skin, lips and nails caused by lack of oxygen to the tissues, breathing difficulty, anxiety, stress and tension. Additional symptoms that may be associated with this disease are joint stiffness and pain and temporarily absent breathing. The diagnosis of ARDS is commonly done by testing for symptomatic signs. A simple chest auscultation or examination with a stethoscope, for example, will reveal abnormal breath sounds which are symptomatic of the condition. Confirmatory tests used in the diagnosis of ARDS include chest X-rays and the measurement of arterial blood gas. In some cases ARDS appears to be associated with other diseases, such as patients with acute myelogenous leukemia, who developed acute tumor lysis syndrome (ATLS) after treatment with cytosine arabinoside. In general, however, ARDS appears to be associated with traumatic injury, severe blood infections such as sepsis, or other systemic illness, the administration of high dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure, and in many cases death. In premature babies ("primies"), the lungs are not quite developed and, therefore, the fetus is in an anoxic state during development. In addition, lung surfactant is generally yet not present in sufficient amounts at this early stage of life. However, premies often hyper-express the adenosine A₁ receptor and/or underexpress the adenosine A22 receptor and are, therefore, susceptible to diseases and conditions such as bronchoconstriction, lung inflammation, and ARDS, among others. Respiratory distress syndrome (RDS) occurring in the preterm infant is an extremely serious problem. A primary cause of RDS in such preterm infants is the immature developmental stage of the infant, resulting in lack of surfactant, a material critical for normal respiration. Preterm infants exhibiting RDS are ventiliated, and administered oxygen and surfactant preparations. Infants with RDS, when they survive, frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease of early infancy. This too is often fatal.

The death rate from ARDS exceeds 50%. Although many survivors recover normal lung function, some individuals may suffer permanent lung damage, which ranges from mild to severe. Moreover, ARDS patients are often afflicted with complications, such as multiple organ system failures. Up to the present time, no measures to prevent or treat ARDS are known. Recently, however, it was reported that an increase in the ratio of certain fatty acid by-products of phosphatydic acid metabolism is predictive of the likelihood that a patient will develop ARDS and that, furthermore, the predictive value of the index correlates with the severity of the illness. Remedial treatment is limited to compensating for the severe dysfunction of the respiratory system and treating the underlying cause of the lung injury. One of the fastest developing symptoms in ARDS is hypoxia, which is generally treated by administration of hyperbaric oxygen, often at high concentrations, many times 100% oxygen concentrations are needed. This is done in many circumstances by necessity by means of intubation or by passing a tube through the nose or the mouth of the patient into the trachea (airway). In addition, mechanical ventilation or a respirator, a machine used to aid the breathing, is usually necessary for further supporting the respiratory system. This treatment may need to be continued until a gradual weaning from the mechanism is

tolerated. Although no therapeutic treatment of ARDS itself exists at the present time, other medications may be administered to treat infection, reduce inflammation and eliminate fluid within the lungs. The minimal daily chores become tremendously difficult to perform under the circumstances, and often the sole recommendation doctors can offer to ARDS patients is that they join support groups to share common experiences and problems with other ARDS victims. As already indicated, respiratory distress syndrome also occurs in premies and infants. Thus, in view of the potential for predicting whether or not a patient may develop ARDS, it becomes even more important to make available a novel strategy to treat Acute Respiratory Disorder Syndrome (ARDS), because now it has become possible to apply it to the prevention of ARDS as well, be it in adults, in children, or in prematurely born babies ("primies").

Adenosine, in addition, slows the conduction time through the heart's A-V node, may interrupt the reentry pathways through the A-V node, and may restore normal sinus rhythm in patients with paroxymal supraventricular tachycardia (PSVT), more commonly described as supraventricular tachycardia (SVT), including that associated with Wolff-Parkinson-White Syndrome. The systemic administration of adenosine was found useful for treating SVT, and as a pharmacologic means to evaluate cardiovascular health via an adenosine stress test commonly administered by hospitals and by doctors in private practice. Adenosine administered by inhalation is known to cause bronchoconstriction in asthmatics, possibly due to mast cell degranulation and histamine release, effects which have not been observed in normal subjects. Adenosine infusion has caused respiratory compromise in patients with obstructive pulmonary disease. As a consequence of the untoward side effects observed in many patients, caution is recommended in the prescription of adenosine to patients with a variety of conditions, including obstructive lung disease, emphysema, bronchitis, etc, and complete avoidance of its administration to patients with or prone to bronchoconstriction or bronchospasm, such as asthma. In addition, the administration of adenosine must be discontinued in any patient who develops severe respiratory difficulties.

Allergic rhinitis afflicts one in five Americans, accounting for an estimated \$4 billion in health care costs each year: \$2 billion for the seasonal variant and more than \$2 billion for the perennial variant. If associated airway diseases are considered, the cost may approach \$10 billion. But even this enormous figure may underestimate the disorder's true toll. Because many people mislabel their symptoms as persistent colds or sinus problems, allergic rhinitis is probably underdiagnosed. If other associated airway diseases are considered, the cost may approach \$10 billion. But even this enormous figure may underestimate the disorder's true toll. Because many people mislabel their symptoms as persistent colds or sinus problems, allergic rhinitis is probably underdiagnosed. Rhinitis can occur at any age. Typically, IgE combines with allergens in the nose to produce chemical mediators, induction of cellular processes, and neurogenic stimulation, causing an underlying inflammation. Symptoms include nasal congestion and discharge, sneezing, and itching. Sufferers also may have itchy, watery, swollen eyes. Over time, allergic rhinitis may predispose sufferers to the development of sinusitis, otitis media with effusion, and nasal polyposis. In addition, rhinitis can exacerbate asthma. Allergic rhinitis also can be associated with mood and cognitive disturbances, fatigue and irritability. Many medications may produce adverse reactions-such as sedation with some over-the-counter anti-histamines-that could further impair a patient's quality of life. An understanding of the pathophysiology of the nose will often dictate appropriate therapy. Cholinergic pathways, when stimulated, produce typical secretions that can be identified by their glandular constituents so as to implicate neurologic stimulation. Secretions typical of

increased vascular permeability are found in allergic reactions as well as upper respiratory infections. Degranulation of mast cells results in the release of preformed mediators that interact with various cells, blood vessels, and mucous glands to produce the typical rhinitis symptoms. Most early- and late-phase reactions occur in the nose after allergen exposure. The late-phase reaction is seen in chronic allergic rhinitis, with hypersecretion and congestion as the most prominent symptoms. Priming can occur; it is characterized by a lowered threshold to stimulus after repeated allergen exposure. This repeated exposure causes a hypersensitivity reaction to one or many allergens. Sufferers may also become hyperreactive to nonspecific triggers such as cold air or strong odors. Rhinitis may be seasonal or perennial, allergic or nonallergic. Nonallergic rhinitis can be induced by infections, such as viruses, or associated with nasal polyps, as occurs in patients with aspirin idiosyncrasy. Medical conditions such as pregnancy or hypothyroidism can cause rhinitis, as can exposure to occupational factors or medications. The so-called NARES syndrome is a nonallergic type of rhinitis associated with eosinophils in the nasal secretions. It typically occurs in middle-aged individuals and is accompanied by some loss of sense of smell. Ideally, attempts should be made to minimize contact with the suspected allergen. If dust mite sensitivity is suspected, using allergen-proof covers for the mattress and pillows can improve symptoms. Washing sheets in hot water and removing carpets and drapes are other helpful strategies for reducing dust mite exposure. Saline alone can improve nasal stuffiness, sneezing, and congestion saline sprays usually cause no side effects and may be tried first in pregnant patients. Saline sprays are generally used to relieve mucosal irritation or dryness associated with various nasal conditions, minimize mucosal atrophy, and dislodge encrusted or thickened mucus. Also, if used immediately before intranasal corticosteroid dosing, saline sprays may help prevent drug-induced local irritative side effects. Antihistamines often serve as a foundation of symptomatic therapy. Terfenadine and astemizole, two nonsedating antihistamines, have been associated with a ventricular arrhythmia known as Torsades de Points, usually in interaction with other medications such as ketoconazole and erythromycin, or secondary to an underlying cardiac problem. To date loratadine, another nonsedating antihistamine, and cetirizine have not been associated with an adverse impact on the QT interval, or with adverse cardiovascular events. The most common side effect of cetirizine is drowsiness (14% vs. 6% on placebo). When used in recommended doses by patients without known risk factors, the non-sedating anti-histamines generally pose minimal risk for an adverse cardiac event. These drugs, e.g. Claritin, can be effective in relieving sneezing, runny nose, and nasal, ocular and palatal itching. Although not approved for this indication, some of the non-sedating agents may be useful in patients with asthma. Studies indicate that terfenadine, loratadine and astemizole exhibit modest bronchodilating effects, reduce bronchial hyperreactivity to histamine, and protect against exercise- and antigen-induced bronchospasm, although some of these benefits may require higher-than-currently-recommended doses. The sedating-type antihistamines may help people to sleep at night, but they cause sleepiness and compromise performance if taken during the day. Antihistamines are typically combined with a decongestant to help relieve nasal congestion. Sympathomimetic medications are used as vasoconstrictors and decongestants. The three common systemic decongestants are pseudoephedrine, phenylpropanolamine and phenylephrine. These agents may cause hypertension, palpitations and tachycardia, as well as restlessness, insomnia and headache. The interaction of phenylpropanolamine with caffeine-in doses of two to three cups of coffee-may significantly raise blood pressure. In addition, medications such as pseudoephedrine can cause hyperactivity in children. Topical decongestants should be used only for a limited period of time, as they

are associated with a rebound nasal dilatation with overuse. Anticholinergic agents have a role in patients with significant rhinorrhea or for specific entities such as "gustatory rhinitis," which is usually associated with ingestion of spicy foods. They also have been studied for their beneficial effects on the common cold. Cromolyn has a good safety record and is especially effective if used prophylactically. Administered via nasal spray, cromolyn can be effective in reducing sneezing, rhinorrhea, and nasal pruritus. It can block both early- and late-phase hypersensitivity responses. Although side effects are unusual, sometimes the spray will produce sneezing, transient headache, and even nasal burning. Topical corticosteroids such as Vancenase are very effective agents in the treatment of rhinitis, especially for symptoms of congestion, sneezing, and runny nose. Depending on the preparation, the corticosteroid nose sprays may cause irritation, stinging, burning, or sneezing. Local bleeding and septal perforation can also occur, especially if the aerosol is not aimed in the proper direction. Topical steroids generally are more effective than cromolyn sodium, and are particularly effective in the treatment of NARES. These agents can be highly effective in reducing the symptoms of rhinitis, but side effects limit their usefulness except for temporary therapy in patients with severe symptoms. These agents are particularly useful in shrinking nasal polyps when local therapy has been unsuccessful. Immunotherapy, while expensive and inconvenient, often can provide substantial benefits, especially for patients who experience side effects from other medications. The therapy is associated with production of so-called blocking antibodies, and with an alteration of cellular histamine release. Eventually, these changes result in decreased IgE, along with many other favorable physiologic changes. Because of the rising prevalence of IgE-mediated diseases, it is important to note the possible role of IgE-mediated hypersensitivity in atopic patients who suffer from recurrent middle ear infections. For allergic rhinitis sufferers, a runny nose is more than a nuisance. The disorder can impair quality of life and set the stage for more serious ailments including psychological problems. But it may be controlled. Presently available treatments may help to minimize symptoms, such as propranolol, verapamil, and adenosine. These have Food and Drug Administration-approved labeling for acute termination of supraventricular tachycardia (SVT).

Verapamil has been the most commonly used agent in the general population but it has several shortcomings, such as its potential to cause or exacerbate systemic hypotension, congestive heart failure, bradyarrhythmias, and ventricular fibrillation. In addition, verapamil readily crosses the placenta and has been shown to cause fetal bradycardia, heart block, depression of contractility, and hypotension. Adenosine has several advantages over verapamil, including rapid onset, brevity of side effects, theoretical safety, and probable lack of placental transfer. Adenosine ultimately may prove to be the preferred agent for termination of paroxysmal supraventricular tachycardia also in the gravid woman. Given the high numbers of deaths involving myocardial disease, the possibility of identifying individuals who are at risk is of great importance, because an early detection permits an early treatment of the conditions. Electrocardiographic stress tests are used for this purpose while an individual exercises, but they lack high sensitivity and specificity. This is particularly the case with asymptomatic patients or with those with atypical toracic chest pain of angina. In this case, in addition to the excercise stress test, cardiac perfusion images are also obtained with  $\gamma$  rays, such as those emitted by 201 Th or 99 mTc. A good number of coronary patients, however, cannot excercise at a level acceptable to validate the results of the test, such as those afflicted with severe arthritis and peripheral vascular diseases or conditions, among others. Hypertensive patients taking β-blockers and calcium channel antagonists also present a

problem as to the detection of an adequate pulse and an effective stress test result while exercising. It is for these groups of patients who may not exercise adequately that pharmacological stress tests are most useful. In the United States about a third of patients referred for myocardial perfusion tests are administered pharmacological tests. For these, as well as for patients attended to in general practice, two kinds of drugs are utilized: coronary vasodilating drugs and positive inotropic agents.

Only two coronary dilating agents have been approved by the FDA for use in this test: dipyrimidol and adenosine, both of which dilate coronary arteries by elevating the level of adenosine in blood and increasing 4 or 5-fold the coronary blood flow. Once these changes are imparted, the patient is administered intravenously a radioactive agent, such as 201Ta or 99mTc to do y-ray imaging. Although in a normal person the distribution of the radiolabel would be uniform, in a subject with one or more stenosis or occlusions in the coronary arteries will exhibit areas or "defects" in the artery (ies) irrigated by the radioactive label of different intensity (ies), which is attributtable to ischemia or to myocardial necrosis. Contrary to those observed with exercise, the hemodynamic and electrocardiographic changes observed upon the administration of pharmacological agents like adenosine are slight. Usually the pulse will increase from 10% to 20% and the systemic arterial pressure from 5% to 10%, and the electrocardiographic depressions of the CT segments in the electrocardiogram (ECG) indicate a specific and serious sign of coronary artery disease. Thus, for many patients, the ability to undergo a pharmacological stress test is of extreme importance. However, many patients exhibit secondary effects (side effects), which in many cases result in severe bronchospasm, myocardial infarction and death. Thus, the administration of adenosine in a pharmacologic stress test is contraindicated in individuals afflicted with bronchoconstriction, asthma, including occult asthma, hypotension, and atrioventricular blockage of the second and third degrees. Many SVT patients and other subjects who would benefit from adenosine administration to assess their cardiovascular function, however, have hyper-responsive airways and are, thus, prone to bronchoconstriction in response to the administration of adenosine. This by itself, prevents them from being administered adenosine in order to avoid extreme bronchoconstriction, which may be life threatening.

The availability of a novel strategy to prevent and/or counter adenosine receptor-associated effects of disorders and conditions associated with symptoms such as pulmonary bronchoconstriction, impeded respiration, inflammation and allergy (ies), among others, of great practical importance. Such technology is clearly applicable to the treatment of heart, lung and kidney damage or failure, e.g. associated with hypoxia ailments including Acute Respiratory Disorder Syndrome (ARDS), asthma, distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer, would clearly find an immediate therapeutic application. Similarly, a composition and method which are suitable for administration before, during and after other treatments or diagnostic procedures, including radiation, chemotherapy, administration of radiocontrast agents, including those containing metal ions, antibody therapy, phototherapy and cancer, and other types of surgery, and adenosine such as in stress tests and in the treatment of SVT, among others, that may be effectively administered preventatively, prophylactically or therapeutically, and in conjunction with

other therapies, or by itself for conditions without known therapies or as a substitute for therapies that have significant negative side effects is also of immediate clinical application.

#### **SUMMARY OF THE INVENTION**

The present invention relates to a pharmaceutical composition, which has cardiopulmonary and/or renal protective activity or which is effective for preventing or treating diseases and conditions such as ARDS, and those associated with ischemia or the release of endotoxins or with the administration of certain agents, including adenosine, e.g. for treating SVT, etc. Examples of these are septic and toxic shock and septicemia. The main component of the composition is a nucleic acid which comprises an oligonucleotide (oligo), which when administered to a subject is effective for alleviating or inhibiting the adenosine-mediated diseases and conditions described and many others. The oligos are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions such as intron and exon borders, e.g. the 5' end, the 3' end and the juxta-section between coding and non-coding regions, or to all segments of mRNA(s) encoding an adenosine A₁, A_{2a}, A_{2b} and A₃ receptors having A₁, A_{2b} and/or A₃ agonist activity or A_{2a} antagonist activity, (generally to any agent having adenosine A_{2a} agonist activity), anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions such as intron and exon borders selected from the group consisting of the 5' end, the 3' end or the juxta-section between coding and non-coding regions, or to analogues to these oligos consisting of less than about 15% adenosine (A), or mixtures thereof, and a physiologically acceptable carrier, and other agents such as diagnostic agents, e.g. radio-contrast media, other therapeutic agents for treating diseases or conditions or exogenous compounds which are associated with lung, heart or renal damage, e.g., glycerol, endotoxin and chemotherapeutic agents such as cisplatin and methotrexate, and formulation ingredients, among others. Examples of adenosine administration are in the treatment of SupraVentricular Tachycardia (SVT) and in stress tests in hyper-sensitized individuals. Side effects caused by the exogenous administration of adenosine, such as extreme respiratory difficulty, airway blockage, bronchoconstriction, allergy and inflammation, among others, are prevented and countered by the present agents and in some cases, depending on the dose administered, totally abolished. Other diseases or conditions afflict the kidneys and other organs and their functions by increasing levels of endotoxin, and the like. Many diseases and conditions are often associated with the development of ischemia or hypoxia which, by itself or through the release of other agent(s), is either associated with or brings about cardiopulmonary or renal damage and/or failure, and thus may benefit from the present invention as applied to protect the heart and kidneys. Thus, the pharmaceutical composition of the invention may be used to protect the lungs, heart and kidneys from damage associated or caused by other diseases or conditions or the administration of therapeutic or diagnostic agents. In addition, the present composition may also be applied to the treatment of numerous conditions which, in its absence, might produce considerable heart, lung and kidney damage and even failure, by addition of one or more therapeutic agents for treating the disease or condition as well as the agent described in this patent. For example, a pharmaceutical composition in accordance with the invention might comprise an anti-cancer agent and the lung, heart and kidney protecting agent of the invention, in amounts effective for treating cancer and for preventing kidney damage, respectively. In another example, the present agent in combination with other therapeutic agents, including anti-cholinergic agents, and the like, may be used to treat food poisoning when endotoxins are released by microorganisms such as the Botulinium family and others, or to treat snake poisoning such as when endotoxin is released, etc., while protecting the subject from the effects of endotoxins, including septic shock and septicemia. Similarly, the present composition may be utilized to protect a subject from renal damage while conducting a diagnostic procedure containing an agent which has deleterious pulmonary, cardiac and/or renal effects, by separately administering or combining in one composition the agent of the invention and a diagnostic agent. The present composition is also suitable for treating harm associated with the administration of substances like adenosine, cysplatin, radiocontrast agents and glycerol, routinely used for diagnostic and therapeutic purposes.

The agents of this invention may be formulated for administration by various different routes, such as topical and systemic, e.g. oral, parenteral, inhalable, and the like, and are generally administered in amounts which prevent or reduce adenosine-mediated side effects such as bronchoconstriction, allergy(ies), inflammation and airway obstruction, among others. The present compositions and formulations, thus, are suitable for the prevention and alleviation of adenosine-mediated bronchoconstriction, allergy and/or inflammation, which are associated with the administration of adenosine in the treatment of SVT and in stress tests to hyper-sensitized individuals. These agents may be administered by themselves or in conjunction with adenosine or similar acting drugs, and in a preventative as well as therapeutic course.

The present composition and formulations may thus be applied to the prevention or alleviation of adenosine receptor-mediated cardiopulmonary and/or renal damage or failure, such as occurs in subjects afflicted with ischemia and as a consequence of the administration or release in the organism of certain compounds such as glycerol, endotoxin, cisplatin, or radiocontrast agents used for imaging purposes, or other agents which are administered for therapeutic or diagnostic purposes, or as a consequence of an accident. The formulations of this invention, e.g. topical, oral, parenteral, inhalable, and the like, also reduce adenosine-mediated bronchoconstriction and/or help to prevent or treat ARDS symptoms. The formulations may be administered to a subject by themselves or in conjunction with other therapies that are known in the art. The present composition is effective to alleviate bronchoconstriction, lung allergy(ies) and inflammation, cardiopulmonary and renal diseases and conditions, e.g. renal damage and faulure, hypoxia, ARDS, COPD, etc., as well as cardiopulmonary effects (deleterious) associated with the administration of certain diagnostic and therapeutic agents, and optionally comprising a surfactant, and the oligo described here. Generally, the oligos are anti-sense to an adenosine A1, A2a, A2b or A3 receptor and exhibit adenosine A₁, A_{2b} or A₃ receptor inhibitory activity or adenosine A_{2a} agonistic activity, and analogues thereof wherein A is substituted by a universal base that binds to thymidine. Moreover, any adenosine A2 agonist is encompassed by this invention, not only anti-sense oligos. These analogues evidence either reduced adenosine content or reduced adenosine receptor activating activity. The above composition is generally administered in an amount which prevents or reduces adenosine receptor associated side effects such as bronchoconstriction, allergy(ies), inflammation and airway obstruction, lung, heart and kidney damage, among others. The present compositions and formulations, thus, are suitable for the prevention and alleviation of adenosine receptor associated bronchoconstriction, allergy and/or inflammation and, therefore, in the treatment of Acute Respiratory Disorder Syndrome (ARDS), asthma, side effects associated with adenosine administration in SupraVentricular Tachycardia (SVT) and in stress tests to hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary

vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer, among others. These compositions are also suitable for use in the prevention and treatment of adenosine-receptor mediated effects brought about by the administration of exogenous agents. The present technology is also applicable in conjunction with other procedures and/other therapies, including other therapeutic agents such as antibody therapy and chemotherapy, among others, radiation, phototherapy, and cancer and other types of surgery, and is effectively administered preventatively, prophylactically or therapeutically. The present pharmaceutical formulations may be administered to a subject in need of such treatment in amounts comprising an anti-renal damage or failure effective amount of the oligo of the invention, and optionally other agents having specific activities, carriers and other formulation ingredients as known in the art.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

Figures 1A to 1D illustrate the effects of A₁ adenosine receptor anti-sense oligonucleotides and mismatch control anti-sense oligonucleotides on the dynamic compliance of the bronchial airway in a rabbit model. The two stars represent significant difference at p<0.01, Student's t-test.

Figures 2A and 2B illustrate the specificity of  $A_1$  adenosine receptor anti-sense oligonucleotides as indicated by the number of  $A_1$  (Figure 2A) and  $A_2$  (Figure 2B) adenosine receptors present in airway tissue treated with  $A_1$  adenosine receptor anti-sense oligonucleotides.

Figures 3A and 3B illustrate the response of two hyper-responsive monkeys (ascaris sensitive) to a challenge with inhaled adenosine. The right hand bar represents the PC₄₀ adenosine after administration of the Oligo I, whereas the left hand bar represents the PC₄₀ adenosine value prior to treatment with the Oligo I. The PC₄₀ adenosine, represented in the Y axis, is the amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways. Figure 3A represents the experimental results obtained without and with pre-treatment of a first monkeys with a phosphorothioate agent of the invention (anti-sense oligo I; SEQ. ID NO: 1), prior to administration of adenosine. Figure 3B represents the experimental results obtained without and with pre-treatment of a second monkey with a phosphorothioate agent of this invention (anti-sense oligo I; SEQ. ID NO:1), prior to administration of adenosine.

Figure 4 shows the effect on surfactant in an experimental animal. In the Figure, the square 1 shows the baseline level of surfactant in the rabbit. Square 2 shows the level of surfactant after administration of adenosine (Post adenosine challenge). Square 3 shows the level of surfactant upon administration of an adenosine A₁ anti-sense oligonucleotide (SEQ. ID NO:1) and then adenosine.

Figure 5 shows the effect on a rabbit BAL fluid of saline, endotoxin alone and endotoxin following Oligo I (SEQ. ID NO: 1) on the number of circulating neutrophils.

Figure 6 shows the effect on wet weights of rabbit lungs of endotoxin alone and endotoxin following Oligo I (SEQ. ID NO: 1) on edema (weight difference).

Figure 7 shows the effect on rabbit BAL fluid of saline, endotoxin alone and endotoxin following Oligo I (SEQ. ID NO: 1) on the total number of total cell count.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One aspect of this invention arose from a desire by the inventor to improve on his own prior technology for the treatment of acute bronchoconstriction, allergy and/or inflammation associated with various diseases and conditions and as an improvement on ineffective existing methods for treating diseases and conditions such as Acute Respiratory Distress Syndrome (ARDS), allergic rhinitis, asthma, adenosine administration e.g. in the treatment of SupraVentricular Tachycardia (SVT) and other arrhythmias, and in stress tests to adenosine hyper-sensitized individuals, ischemia, renal damage or failure induced by certain drugs, infantile respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD). and cancers such as leukemias, lymphomas, carcinomas, and the like, including colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all types of cancers which may metastasize or have metastasized to the lung(s), including breast and prostate cancer. Extremely dangerous, and in many cases lethal, effects are encountered when adenosine receptors are activated by adenosine, administration. The activation of the adenosine A, receptor, in particular, may cause life threatening, and in some cases even fatal, bronchoconstriction in hyper-responsive individuals. The inventor, in addition, wanted to provide a treatment which would improve the outcome and life style of patients undergoing other procedures or being administered other therapies, including antibody therapy, chemotherapy, radiation, phototherapy, and surgery e.g. cancer surgery, and that could be effectively administered preventatively, prophylactically or therapeutically.

He succeeded in this endeavor and is providing in this patent novel and improved compositions, formulations and methods which afford greatly improved results when compared with previously known treatments for preventing and alleviating bronchoconstriction, allergy(ies), inflammation, breathing difficulties and blockage of airways, cardiopulmonary and renal damage, and the like. The nucleic acid, and optional surfactant and other components, of the composition of the invention may be formulated alone with a carrier, or with other therapeutic agents and formulation agents as is known in the art. The compositions of this invention, thus, may be incorporated into a variety of formulations for systemic and topical administration.

The present composition and treatment are applicable to avoiding cardiopulmonary and renal damage, such as that seen in association with ischemic or hypoxic conditions as well as with the administration of radio-contrast media, and certain other agents, e.g. those known to cause ischemia and/or to produce cardiopulmonary and/or renal damage or failure, such as such as radiocontrast agents, glycerol and chemotherapeutic agents such as methotrexate and cisplatin. In addition, the inventor found that the present technology is suitable for the prevention and treatment of renal damage and failure such as is produced in food and snake poisoning as well as septicemia and septic or toxic shock caused by the release of endotoxins, such as when microorganisms of the type Botulinum, and the like, are ingested, or even from unknown sources.

To his surprise, the inventor found that the present agent had a protective effect with respect to the heart, lung and kidneys, and that it could be administered prophylactically as well as therapeutically. In addition, when specific other agents are included the present composition may also be applied to the treatment of diseases and conditions where the other agents have a secondary deleterious cardiopulmonary or renal effect, including diseases and conditions associated with ischemia, the

administration of adenosine, e.g. for the treatment of SVT or in stress tests, for the treatment of cancer, e.g. by administration of an anti-cancer drug such as cisplatin and the oligo of this invention. Thus, the anti-sense oligonucleotide (oligo) of the invention may be administered as a variety of formulations, either by itself, with or without a surfactant, or with other agents. The anti-sense oligonucleotide of this invention, thus, may be incorporated into a variety of formulations for systemic and topical administration.

The present invention also improves on the state of the art for rescuing patients afflicted with ARDS, whether as a consequence of multiple traumatic injury, severe blood infections such as sepsis, or other systemic illness, the administration of high dose radiation therapy and chemotherapy, and inflammatory responses which lead to multiple organ failure, and in many cases death. Although a large number of persons are afflicted with this disease or condition every year, up to the present time, no measures to prevent ARDS have been available. ARDS has been and still is considered to be untreatable. and the only palliative treatment has been limited to compensating for the severe dysfunction of the respiratory system and treating the underlying cause of the lung injury. One of the fastest developing symptoms in ARDS is hypoxia, which is generally treated by administration of hyperbaric oxygen, often at high concentrations. The inventor extensively investigated the etiology of Respiratory Distress Syndrome (RDS) and ARDS and other conditions which appear to trigger ARDS, and is hereby proposing the implementation of a prophylactic or preventative and therapeutic treatment based on the administration of oligonucleotides, with or without vectors linked to them designed to treat the acute impairment of the airways, bronchoconstriction, allergy and/or inflammation symptoms seen in patients who develop ARDS. The present composition, formulations and methods are, thus, applicable to the prophylaxis of ARDS immediately after a potential diagnosis is made that a patient is a good candidate for developing the condition. In addition, and given that ARDS symptoms many times develop extremely fast, the present technology is also applicable to the treatment of patients who are already afflicted with the respiratory and inflammatory symptoms seen in ARDS. The present composition and formulations may be administered by themselves or in conjunction with other ancillary agents directed to alleviating ARDS symptoms, such as oxygen-enriched air, surfactants, blood pressure controlling agents, and the like. The composition of the invention is provided in a variety of formulations for systemic and topical administration, which may utilized as prescribed by a clinician.

The present inventor unexpectedly found that the agents of the invention, particularly those which have at least some inhibitory activity over the adenosine A₁ receptor, strongly inhibit, and in some cases terminate, with 100% efficacy, the acute respiratory and inflammatory symptoms of ARDS. Experimental work, some of which is provided in the examples of this patent, has shown a complete interference with, and cessation of, bronchoconstriction and other unwanted side effects associated with ARDS, which are mediated by adenosine receptor(s) in each of two animal models of human bronchial hyper-responsiveness: a hyper-responsive rabbit model and a hyper-responsive cynamologous monkey model, both being widely acknowledged by the scientific community as models for bronchoconstriction, allergy and inflammation involving the respiratory airways in humans. The agents of this invention, therefore, have been shown to prevent and counter these ARDS-associated symptoms, associated with adenosine receptors, possibly with an adenosine A₁ receptor. The prevention and suppression of ARDS symptomatology seen upon administration of the agent of this invention is clearly applicable to the prevention of ARDS and to the treatment of patients afflicted by this condition by itself, either prior to,

simultaneously with, and subsequent to other palliative therapy. The present invention now is set to save a large number of previously unnecessarily lost lives, given the high morbidity and mortality associated with ARDS.

Respiratory distress syndrome (RDS) occurs in preterm infants ("preemies"), and is an extremely serious problem. A primary cause of RDS in such preterm infants is the immature developmental stage of the infant, resulting in low levels or lack of surfactant, a material critical for normal respiration. Preterm infants or "premies" exhibiting RDS are ventiliated, and administered oxygen and surfactant preparations. When they survive, infants with RDS frequently develop bronchopulmonary dysplasia (BPD), also called chronic lung disease (CLD) of early infancy. This condition too is often fatal.

The causes of surfactant depletion in the preterm infant are unknown. However, it is known that surfactant secretion is upregulated through adenosine A2a receptors and inhibited through adenosine adenosine A₁ receptors. It has been shown that ATP and A₁ adenosine receptor agonists mobilize intracellular calcium and activate potassium and chloride currents in normal and cystic fibrosis airway epithelial cells. Furthermore, the adenosine A₁ receptor is also known to participate in the protection of tissues from the effects of oxygen deprivation or hypoxia. Based on these and other pieces of information, the inventor hypothesized that, during normal fetal development, there is a changing (increasing) ratio of the adenosine A_{2a} receptor to the adenosine A₁ receptor (A_{2a}:A₁ ratio), such that the A₁ receptor protects fetal lung tissues during fetal anoxia and inhibits premature surfactant secretion. The adenosine A₁ receptor expression decreases as the fetus approaches term. Conversely, he hypothesized that the adenosine A_{2a} receptor is less expressed in early fetal stages, and its expression increases as the fetus approaches term, ensuring normal levels of surfactant secretion upon birth. In the pre-term infant, an existing high adenosine A₁:A_{2a} ratio does not have an opportunity to reverse itself because the infant is born before adequate adenosine A_{2a} receptor expression occurs and while there is still significant adenosine A₁ expression. This causes decreased surfactant production at birth and thereafter. Accordingly, he surmised that the administration of an adenosine A₁ anti-sense oligonucleotide would reduce the level of adenosine A₁ receptor formed. In addition, he also surmised that the administration of any adenosine A22 agonist, whether or not an oligonucleotide, would specifically stimulate this receptor. Either therapy or a combination of both would be suitable for treating RDS, particularly in "preemies."

Rhinitis is not a disease, it is a term describing a group of symptoms produced by nasal irritation or inflammation. Allergies, however, including allergic rhinitis, affect an estimated 40 to 50 million people in the United States. Some allergies may interfere with day-to-day activities or lessen the quality of life. Rhinitis is a term describing the symptoms produced by nasal irritation or inflammation. Symptoms of rhinitis include runny nose, itching, sneezing and stuffy nose due to blockage or congestion. These symptoms are the nose's natural response to inflammation and irritation. Arbitrarily, rhinitis lasting less than six weeks is called acute rhinitis, and persistent symptoms are called chronic rhinitis. Acute rhinitis is generally caused by infections or chemical irritation. Chronic rhinitis may be caused by allergy or a variety of other factors. The nose normally produces mucus, which traps substances like dust, pollen, pollution, and germs such as bacteria and viruses. Mucus flows from the front of the nose and drains down the back of the throat. When mucus production is excessive, it can

flow from the front, as a runny nose, or become noticeable from the back, as post-nasal drip. Nasal mucus, normally a thin, clear liquid, can become thick or colored, perhaps due to dryness, infection or pollution. When post-nasal drip is excessive, thick, or contains irritating substances, cough is the natural response for clearing the throat. Itching and sneezing are also natural responses to irritation caused by allergic reactions, chemical exposures including cigarette smoke, or temperature changes, infections and other factors. The nasal tissues congest and decongest periodically. In most people, nasal congestion switches back and forth from side to side of the nose in a cycle several hours long. Some people, especially those with narrow nasal passages, notice this nasal cycle more than others. Strenuous exercise or changes in head position can affect nasal congestion. Severe congestion can result in facial pressure and pain, as well as dark circles under the eyes. Sinusitis is inflammation or infection of any of the four groups of sinus cavities in the skull, which open into the nasal passages. Sinusitis is not the same as rhinitis, although the two may be associated and their symptoms may be similar. The terms sinus trouble or sinus congestion are sometimes wrongly used to mean congestion of the nasal passage itself. Most cases of nasal congestion, though, are not associated with sinusitis. Known to most people as hay fever, allergic rhinitis is a very common medical problem affecting more than 15 percent of the population, both adults and children. Allergic rhinitis takes two different forms seasonal and perennial. Symptoms of seasonal allergic rhinitis occur in spring, summer and/or early fall and are usually caused by allergic sensitivity to pollens from trees, grasses or weeds, or to airborne mold spores. Other people experience symptoms year-round, a condition called perennial allergic rhinitis. It is generally caused by sensitivity to house dust, house dust mites, animal dander and/or mold spores. Underlying or hidden food allergies are considered a possible cause of perennial nasal symptoms. Some people may experience both types of rhinitis, with perennial symptoms worsening during specific pollen seasons. There are, however, other causes for rhinitis. When a sensitive person inhales an allergen (allergy-causing substance) like ragweed pollen, the body's immune system reacts abnormally with the allergen. The allergen binds to allergic antibodies (immunoglobulin E) that are attached to cells that produce histamine and other chemicals. The pollen " triggers " these cells in the nasal membranes, causing them to release histamine and the other chemicals. Histamine dilates the small blood vessels of the nose and fluids leak out into the surrounding tissues, causing runny noses, watery eyes, itching, swelling and other allergy symptoms. Antibodies circulate in the blood stream, but localize in the tissues of the nose and in the skin. This makes it possible to show the presence of these antibodies by skin testing, or less commonly, by a special blood test. A positive skin test mirrors the type of reaction going on in the nose. Hay fever is a turn-ofthe-century term which has come to describe the symptoms of allergic rhinitis, especially when it occurs in the late summer. However, the symptoms are not caused by hay (ragweed is one of the main culprits) and are not accompanied by fever. So physicians prefer the term "allergic rhinitis" because it is more accurate. Similarly, springtime symptoms are sometimes called rose fever but it's just coincidental that roses are in full-bloom during the grass-pollinating season. Roses and other sweetsmelling, showy flowers rely on bees, not the wind, for pollination, so not much of their pollen gets into the air to cause allergies.

A common question from allergic rhinitis sufferers is whether they may relocate to a place where their allergies will go away. Some allergens are tough to escape. Ragweed which affects 75% of allergic rhinitis sufferers blankets most of the United States. Less ragweed is found in a band along the West Coast, the southern-most tip of Florida and northern Maine, but it is still present. Even Alaska and

Hawaii have a little ragweed. A move may be of questionable value because a person may escape one allergy to ragweed, for example only to develop sensitivity to grasses or other allergens in the new location. Some known complications include ear infections, sinusitis, recurrent sore throats, cough, headache, fatigue, irritability, altered sleep patterns and poor school performance. Occasionally, children may develop altered facial growth and orthodontic problems. In some cases, allergy treatment can eliminate or alleviate most of these problems. Rhinitis may result from many causes other than allergic reaction. Not all rhinitis symptoms are the result of allergies. The following are the three most common causes of rhinitis with some of their characteristics: Rhinitis or Allergic Sensitivity is generally caused by allergic hay fever dust, foods, animals, pollens, molds, perennial and/or seasonal infectious colds or flu viruses, bacteria, and others, and generally lasts 3-7 days. Non-allergic rhinitis may be caused by irritant smoke, air pollution, exhaust fumes, aerosol sprays, fragrance, paint fumes, etc. The most common condition causing rhinitis is the common cold, an example of infectious rhinitis. Most infections are relatively short-lived, lasting from three to seven days. Colds can be caused by any one of more than 200 viruses. Children, particularly young children in school or day care centers, may have from eight to 12 colds each year. Fortunately, the frequency of colds lessens after immunity has been produced from exposure to many viruses. Colds usually begin with a sensation of congestion, rapidly followed by runny nose and sneezing. Over the next few days, congestion becomes more prominent, the nasal mucus may become colored, and there may be a slight fever and cough. Cold symptoms resolve within a couple of weeks, although a cough may sometimes persist. Cold symptoms that last longer may be due to other causes, such as chronic rhinitis or sinusitis. Allergic rhinitis very often has no cure. Most treatments aim at keeping its symptoms under control by avoiding or reducing exposure to substances that cause symptoms and by taking medication when needed.

Dryness of the nasal tissues can be a normal effect of aging, or a characteristic of a nasal condition associated with a foul smelling nasal discharge. Rhinitis can also be a feature of endocrine disease, like hypothyroidism, or can occur during pregnancy. Rhinitis can be made worse or even improved during pregnancy. Alcoholic beverages can cause the blood vessels in the nose to enlarge temporarily and produce significant nasal congestion. Sometimes several conditions can coexist in the same person. In a single individual, allergic rhinitis could be complicated by vasomotor rhinitis, septal deviation (curvature of the bone separating the two sides of the nose) or nasal polyps. Use of spray decongestants for chronic sinusitis, septal deviation or vasomotor rhinitis may cause rhinitis medicamentosa. Any of these conditions will be made worse by catching a cold. Nasal symptoms caused by more than one problem can be difficult to treat, often requiring the cooperation of an allergistimmunologist and an otolaryngologist (ear, nose and throat specialist). Once allergic rhinitis is diagnosed, treatment options include avoidance, medication and immunotherapy (allergy shots), neither of which offers a complete cure. A single ragweed plant may release one million pollen grains in just one day. The pollen from ragweed, grasses and trees is so small and buoyant that the wind may carry it miles from its source. Mold spores, which grow outdoors in fields and on dead leaves, also are everywhere and may outnumber pollen grains in the air even when the pollen season is at its worst. While it's difficult to escape pollen and molds, exposure may be lessened by keeping windows closed, using air-conditioning in the summer and a HEPA (High Energy Particulate Air) filter or an electrostatic precipitator to clean pollen and mold from the air. Early morning is a good time to limit outdoor activities because outdoor air is most heavily saturated with pollen and mold between 5 and 10 a.m., etc. Other than avoidance

measures, medications such as antihistamines and decongestants are the most commonly used for allergic rhinitis. Newer medications, such as cromolyn, inhibit the release of chemicals that cause allergic reactions. Nasal corticosteroid sprays reduce the inflammation from the allergic trigger. Medications help to alleviate nasal congestion, runny nose, sneezing and itching. They are available in many forms, including tablets, nasal sprays, eye drops and liquids. Most of these medications cause side effects. Allergen immunotherapy, known as allergy shots may be recommended for persons who don't respond well to treatment with medications, experience side-effects from medications or have allergen exposure which is unavoidable. Immunotherapy, however, does not cure allergies but can be very effective in controlling allergic symptoms. Allergy injections are usually given at variable intervals over a period of three to five years. An immunotherapy treatment program may consist of injections of a diluted allergy extract, administered frequently in increasing doses until a maintenance dose is reached. Then, the injection schedule is changed so that the same dose is given with longer intervals between injections. Immunotherapy helps the body build resistance to the effects of the allergen, reduces the intensity of symptoms caused by allergen exposure, and sometimes can actually make skin test reactions disappear. As resistance develops, symptoms should improve, but the improvement from immunotherapy will take several months to occur. Immunotherapy does not help the symptoms produced by non-allergic rhinitis.

Antihistamines are the most inexpensive and commonly used treatment for rhinitis. These medications counter the effects of histamine, the irritating chemical released within your body when an allergic reaction takes place. Although other chemicals are involved, histamine is primarily responsible for causing the symptoms. Antihistamines do not cure, but help relieve: nasal allergy symptoms, such as sneezing, itching and discharge; eye symptoms, such as itching, burning, tearing, and clear discharge; skin conditions, such as hives, eczema, itching and some rashes; and other allergic conditions as determined by your physician. There are dozens of different antihistamines and wide variations in how patients respond to them. Some are available over-the-counter and others require a prescription. Generally, they work well but produce side effects. The body tends to build up resistance to some antihistamines over time. This tendency varies from individual to individual. Persons with nasal dryness or thick nasal mucus should avoid taking antihistamines without consulting a physician. Contact your physician for advice if an antihistamine causes drowsiness or other side effects. Short-acting antihistamines can be taken every four to six hours, while timed-release antihistamines are taken every 24 hours. The short-acting antihistamines are often most helpful taken 30 minutes before anticipated allergic exposure (picnic during ragweed season). Timed-release antihistamines are better suited to chronic (long-term) use for those who need daily medications. The most common side effect is sedation or drowsiness. For this reason, it is important that you do not drive a car or work with dangerous machinery the first time you take an antihistamine. You should take the antihistamine for the first time at home, several hours before bedtime. When you are sure that the medicine will not cause sedation, you then can take it any time as prescribed during the day. In persons who experience drowsiness, the sedation effect usually lessens over time. Some of the newer antihistamines produce low drowsiness. Another frequently encountered side effect is excessive dryness of the mouth, nose, and eyes. Less common side effects include restlessness, nervousness, over excitability, insomnia, dizziness, headaches, euphoria, fainting, visual disturbances, decreased appetite, nausea, vomiting, abdominal distress, constipation, diarrhea, increased or decreased urination, high or low blood pressure, nightmares

(especially in children), sore throat, unusual bleeding or bruising, chest tightness or palpitations. Alcohol and tranquilizers increase the sedation side effects of antihistamines and, therefore, must be avoided during therapy.

Decongestants help relieve the stuffiness and pressure caused by allergic, swollen nasal tissue. They do not contain antihistamines, so do not cause antihistamine side effects. They do not relieve the other symptoms of allergic rhinitis, such as runny nose, post-nasal drip and sneezing. Decongestants are available as prescription and non-prescription medications and are often seen in combination with antihistamines or other medications. It is not uncommon for patients using decongestants to experience insomnia if taking the medication in the afternoon or evening. If this occurs, a dose reduction may be needed. At times, men with prostate enlargement may encounter urinary problems while on decongestants. Patients using medications for the management of emotional or behavioral problems should discuss this with their physicians before using decongestants. Pregnant patients should also check with their physician before starting decongestants. Non-prescription decongestant nasal sprays work within minutes and last for hours, but may not be used for more than a few days at a time without a physician's order. Oral decongestants are found in many over-the-counter and prescription medications. and may be the treatment of choice for nasal congestion. They don't cause rhinitis medicamentosa, but need to be avoided by some patients with high blood pressure. If you have high blood pressure, you should check with your physician before using them. Non-prescription saline nasal sprays help counteract symptoms of dry nasal passages or thick nasal mucus. Unlike decongestant nose sprays, a saline nose spray can be used as often as needed. Sometimes, your physician may recommend washing (douching) of the nasal passage. Corticosteroids counteract the inflammation caused by the body's release of allergy-causing substances, as well as that caused by other non-allergic factors. Thus, they generally work for many causes of rhinitis symptoms and are sometimes useful for chronic sinusitis. Corticosteroids are sometimes injected or taken orally, but usually on a short-term basis for extremely severe symptoms. Physicians warn that injected or oral steroids may produce severe side effects when used for long periods or used repeatedly and, for this reason, they should be used with extreme caution. In rhinitis, a corticosteroid is much safer when used by spraying it into the nose. Side effects are less common, but may include nasal ulceration, nasal fungal infection, or bleeding. Cromolyn is a medication that blocks the body's release of allergy-causing substances. It does not work in all patients. The full dosage is four times daily, and improvement may take several weeks to occur. Atropine and the related drug ipratropium bromide are sometimes used to relieve the runny nose of rhinitis; in fact, most antihistamines have a slight atropine-like effect. Atropine can be taken orally and as a nasal spray. It is a component of some antihistamine decongestant preparations. Antibiotics are for the treatment of bacterial infections. They do not affect the course of uncomplicated common colds, and are of no benefit for non-infectious rhinitis, including allergic rhinitis. In chronic sinusitis, antibiotics may help only temporarily, and surgery may be needed. Eye allergy preparations are used when the eyes are affected by the same allergens that trigger rhinitis, causing redness, watery eyes and itching. Eye preparations are available as prescription and non-prescription medications.

All of the non-prescription antihistamines (combined with decongestants) are " first generation " antihistamines and generally cause drowsiness, slowed reaction time and dry mouth in most people. Examples are Actifed (and combination products), Alka Seltzer Plus Sinus Allergy Medicine, Allerest (and combination products), A.R.M., BC Cold Powder Multi-Symptom Formula.

Benadryl (and combination products), Chlor-Trimeton (and combination products), Comtrex Multi-Symptom Day/Night, Contac Maximum Strength, Coricidin (and combination products), Dimetane. Dimetapp (and combination products), Drixoral (and combination products), PediaCare Night Rest Cough-Cold Liquid, Sinarest, Sudafed Plus, Tavist (and combination products), Triaminic Allergy, Tylenol Allergy Sinus/Tylenol PM, Vicks NyQuil (and combination products) and Vicks Pediatric Formula 44M Cough & Cold, among others. The following medications are second generation antihistamines and generally do not cause the extreme degree of side effects of first generation antihistamines, such as drowsiness, slowed reaction time and dry mouth. Examples of prescription antihistamines are Allegra, Claritin, Hismanal and Zyrtec. The latter may cause cardiac problems when combined with certain other medications whereas Hismanol has low sedating side effects. The following contain first generation antihistamines and generally cause drowsiness, slowed reaction time and dry mouth: Atarax, Antivert, Dallergy, Naldecon, Periactin, Rynatan, Temaril, Trinalin and Vistaril. The following are examples of non-prescription oral decongestants: Actifed Allergy Daytime, Allerest, Drixoral Non-Drowsy Formula, Efidac/24, PediaCare Infants' Decongestant Drops and Sudafed Tablets. Examples of prescription oral decongestants are DuraVent, Entex LA, Entex PSE, Exgest LA, Respaire, Sinuvent and Guaifed PD. Examples of non-prescription decongestant nasal sprays are Afrin and related products, Cheracol, Dristan, Duration 12-Hour, 4-Way Fast Acting and NTZ Long Acting. Their prolonged use, however, may cause rebound congestion. Other examples are Neo Synephrine and related Privine Vicks Sinex products, Nostril/Nostrilla, Otrivin, and Long-Acting/Vapor/Vaporub/VapoSteam/Vatronol. An example of non-prescription anti-allergy nasal spray is Nasalcrom, and of non-prescription saline nasal sprays are Afrin Saline Mist, Ayr, NaSal Moisturizer AF, Ocean and Salinex. An example of a prescription antihistamine nasal spray is Astelin. Examples of prescription atropine-like nasal sprays are Atrovent and Prescription nasal corticosteroid sprays, which do not contain antihistamines or decongestants. Other therapeutic agents suitable for the treatment of allergic rhinitis are Beconase (Pockethaler and Beconase AQ), Flonase, Nasacort (Nasal Inhaler and Nasacort AQ), Nasalide, Rhinocort and Vancenase (Pockethaler and Vancenase DS). Examples of prescription oral corticosteroids that do not contain antihistamines are Deltasone, Liquid Pred, Medrol, Pediapred and Prelone.

The present inventor surmised that the administration of the present gents would be effective for the treatment of allergic rhinitis whose symptoms are mediated by adenosine receptors. In addition, the inventor showed the effectiveness of the present therapy, for example, on the level of surfactant in the lung in an animal model in which the adenosine  $A_1$  receptor is known to be highly expressed, the allergic rabbit lung. See, Ail, S. et al., Adenosine-induced bronchoconstriction in allergic rabbit model, Am. J. Physiol. 266:L271-277 (1994); Ali, S. et al., Adenosine-induced bronchoconstriction and contraction of airway smooth muscle from allergic rabbits with late-phase airway obstruction: Evidence for an inducible adenosine adenosine  $A_1$  receptor, JPET 268(3):1328-1334 (1994). In the normal lung, the adenosine  $A_1$  receptor is generally not expressed, whereas the adenosine  $A_2$  receptor is expressed. The experimental set-up and results are shown in Example 37 below.

In the past, anti-sense oligonucleotides received considerable theoretical consideration as being potentially useful as pharmacologic agents for the treatment of human disease. R. Wagner, Nature 372: 333-335 (1994). However, it has been difficult to actually apply them to alleviating and curing human

diseases. One important consideration in the pharmacologic application of these molecules has been the failure of various routes of administration to deliver the compounds to its target while avoiding invading the circulation and, therefore, other untargeted tissues which, thus, produces a plethora of side effects. Most in vivo experiments utilizing anti-sense oligonucleotides involved a direct application of the oligo to limited regions of the brain. See, C. Wahlestedt, Trends in Pharmacol. Sci. 15: 42-46 (1994); J. Lai et al., Neuroreport 5: 1049-1052 (1994); K. Standifer et al., Neuron 12: 805-810 (1994); A. Akabayashi et al., Brain Res. 21: 55-61 (1994). Others applied them into the spinal fluid. See, e.g. L. Tseng et al., European J. Pharmacol. 258: R1-3 (1994); R. Raffa et al., European J. Pharmacol. 258: R5-7 (1994); F. Gillardon et al., European J. Neurosci. 6: 880-884 (1994). Such applications, clearly, have no clinical utility due to their invasive nature. Thus, the systemic administration of anti-sense oligonucleotides poses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues.

The systemic administration of anti-sense oligonucleotides also possesses significant problems with respect to their pharmacologic application, not the least of which is the difficulty in selectively targeting disease-involved tissues. The respiratory system, and in particular the lung, as the ultimate port of entry into the organism, however, is an excellent route of administration for anti-sense oligonucleotides. This is so not only for the treatment of lung disease, but also when utilizing the lung as a means for delivery, particularly because of its non-invasive and tissue-specific nature. Thus, local delivery of antisense oligonucleotides directly to the target tissue enables the therapeutic use of these compounds. Fomivirsen (ISIS 2302) is an example of a local drug delivery into the eye to treat cytomegalovirus (CMV) retinitis, for which a new drug application has been filed by ISIS. The administration of a drug through the lung offers the further advantage that inhalation is non-invasive whereas direct injection in to the vitreous of the eye is invasive.

The composition and formulations of this invention have been shown to have an exceedingly high efficacy for preventing and treating a disease or condition associated with bronchoconstriction, difficult breathing, impeded and obstructed lung airways, allergy(ies) and/or inflammation. The examples provided below show a complete inhibition of such adenosine receptor associated symptoms in a rabbit model for human bronchoconstriction, allergy(ies) and inflammation as well as the elimination of the ability of the adenosine receptor agonist par excellence, adenosine, to cause bronchoconstriction in hyper-responsive monkeys, which are animal models for human hyper-responsiveness to adenosine receptor agonists. The pharmaceutical composition and formulations of the invention, therefore, are suitable for preventing and alleviating the symptoms associated with stimulation of adenosine receptors, such as the adenosine A1 receptors. The compositions and formulations of this invention, thus, are also suitable for prevent the untoward side effects of adenosine-mediated hyperresponsiveness in certain individuals, which are generally seen in diseases affecting respiratory activity. Examples of diseases and conditions, which may be treated preventatively, prophylactically and therapeutically with the compositions and formulations of this invention, are pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, Acute Respiratory Distress Syndrome (ARDS), lung, heart and renal damage and failure, e.g. associated with ischemia as well as the administration of certain drugs, side effects associated with adenosine administration, e.g. in SupraVentricular Tachycardia (SVT) and in adenosine stress tests, infantile Respiratory Distress Syndrome (infantile RDS), pain, cystic fibrosis (CF), pulmonary hypertension, allergic rhinitis pulmonary vasoconstriction, emphysema, chronic

obstructive pulmonary disease (COPD), and cancers such as leukemias, lymphomas, carcinomas, and the like, e.g. colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic metastases, etc., as well as all other metastatic cancers, e.g. cancers which metastasized to the lung(s), breast and prostate. The present compositions and formulations are suitable for administration before, during and after other treatments, including radiation, chemotherapy, antibody therapy, phototherapy and cancer, and other types of surgery. The present compositions and formulations may also be administered effectively as a substitute for therapies that have significant negative side effects.

All nucleotide sequences are represented in this patent by a single strand only, and in the 5' to 3' direction, from left to right. All nucleotide and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission, or (for amino acids) by three letter code, in accordance with 37 CFR § 1.822 and established usage. See, e.g., PatentIn User Manual, 99-102 (Nov. 1990) (U.S. Patent and Trademark Office, Office of the Assistant Commissioner for Patents, Washington, D.C. 20231); U.S. Patent No. 4,871,670 to Hudson et al. at col. 3, lines 20-43. The relevant sections of the disclosures of the above cited, and of all other patents and references cited in this patent are incorporated herein by reference.

The method of the present invention may be used as well to reduce adenosine-mediated heart. lung and kidney damage or failure resulting from any reason, including, but not limited to, ischemia, septicemia, septic shock, and the like, the administration of certain compounds such as radiocontrast agents used for imaging and diagnostic purposes, many of which have metal atoms, adenosine used for treating SVT and in stress tests, and the like. The method of the present invention may be used as well to reduce adenosine receptor associated bronchoconstriction in the lungs of a subject for any reason, including, but not limited to, bronchoconstriction, allergy(ies) and/or inflammation, such as those associated with COPD, ARDS, allergic rhinitis, pulmonary vasoconstriction, asthma, the administration of certain exogenous agents, pain, CF, emphysema, and cancer, among others. The compositions and formulations of the invention comprise a surfactant and an oligonucleotide which is anti-sense to the adenosine A₁, A_{2b} and A₃ receptors have shown to be effective in the down-regulation of the adenosine A₁, A_{2a}, A_{2b} or A₃ receptors, respectively, in the cell. Others which are anti-sense to the adenosine A_{2a} receptor are also effective as long as they have some adenosine  $A_1$  inhibitory activity or adenosine  $A_{2a}$ agonist activity. Similarly, non nucleic acid A2a agonists are suitable. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction and other symptoms, is that the compositions and formulations of this invention may be administered directly into the respiratory system of an individual, and even to his\her lungs. In addition, the present treatment may reduce the amount or level of a receptor protein itself rather than merely acting at the receptor as is the case with treatments and/or where the agent is merely an antagonist acting at the receptor site. The selective characteristic of the present compositions and formulations along with their administration by a selected route results in reduced toxicity.

The present composition, formulations and preventative, maintenance and therapeutic methods were designed to be applied to the treatment of side effects elicited by either the exogenous administration of adenosine, of other agents which have unwanted adenosine-like effects described here, or of agents which elicit an endogenous release of adenosine. The agent of the invention may be

administered either alone or with other therapeutic and diagnostic agents including adenosine, dipyrimidol, other adenosine receptor stimulants, adenosine releasing agents, etc. The present compositions and formulations for systemic and topical administration may be administered prior to, in conjunction with, or subsequent to the administration of adenosine or other adenosine receptor active agents.

The present inventors unexpectedly found that the agents of the invention, particularly those which have at least some inhibitory activity over the adenosine A₁ receptor, strongly inhibit, and in some cases terminate, with 100% efficacy, the ability of adenosine to cause bronchoconstriction in hyperresponsive airways. Experimental work, some of which is provided in the examples of this patent, has shown a complete interference with, and cessation of, adenosine's ability to cause bronchoconstriction and other unwanted side effects associated with its activity at the adenosine receptor(s) in each of two animal models of human bronchial hyper-responsiveness: a hyper-responsive rabbit model and a hyperresponsive cynamologous monkey model, both being widely acknowledged by the scientific community as models for adenosine hyper-responsiveness in humans. The agents of this invention, therefore, have been shown to prevent the untoward side effects of adenosine in the hyper-responsive lung mediated via an adenosine A1 receptor. The suppression of adenosine side effects seen upon the agent's administration is clearly applicable to the treatment of hyper-sensitized subjects jointly with adenosine or by itself. either prior to, simultaneously with, and subsequent to adenosine administration to SVT afflicted subjects. In addition, the present agents are also effective for administration to subjects who need to undergo an adenosine stress test but who, prior to this invention, were prevented from the benefits associated with the administration of such test. The present agent now permits the free administration of adenosine or adenosine-like agents to persons with asthma and other respiratory diseases by preventing or alleviating the bronchial, allergic and/or inflammatory side effects produced by them.

To summarize, adenosine is a natural nucleoside which is used in the treatment of paroxysmal supraventricular tachycardia (PSVT or SVT), including SVT associated with Wolff-Parkinson-White Syndrome, and as a pharmacologic means to evaluate cardiovascular health via an adenosine stress test. Many SVT patients and candidates for adenosine stress testing have hyper-responsive airways associated with the over-expression of adenosine receptors, particularly the adenosine A₁ receptor. When activated by adenosine, the A₁ receptor may cause life threatening, and in some cases even fatal, bronchoconstriction in hyper-responsive airways. The present invention, therefore, permits therapeutic and diagnostic uses of adenosine in subjects whose health and well being would have been previously threatened by administration of adenosine, such as asthmatics and those afflicted by other conditions associated with hyper-responsiveness to this compound.

One of the present agents, i.e. Oligo I (SEQ. ID NO:1; EPI 2010) was shown to be effective in single-handedly eliminating with virtually 100% efficacy the ability of adenosine to cause bronchoconstriction in hyper-responsive airways. The complete termination of the ability of adenosine to cause bronchoconstriction is shown in the exemplary disclosure in two animal models of human bronchial hyper-responsiveness: the hyper-responsive rabbit and the hyper-responsive cynamologous monkey. The oligos of this invention, therefore, are suitable for preventing untoward side effects of adenosine administration in the hyper-responsive lung.

As used herein, the terms "prevent", "preventing", "treat" or "treating" refer to a preventative or

therapeutic treatment which decreases the likelihood that the subject administered such treatment will manifest symptoms associated with adenosine receptor stimulation. The term "down-regulate" refers to inducing a decrease in production, secretion or availability and, thus, a decrease in concentration, of intracellular adenosine A₁, A_{2b} or A₃ receptor or an increase in concentration of the adenosine A_{2a} receptor. Also suitable is the use of A_{2a} agonists. Although the present invention is primarily concerned with the treatment of human subjects, it is also applicable to the treatment of animals, such as other vertebrates, including mammals, large and small, wild and domesticated, including pets, e.g. dogs and cats, for veterinary purposes. In general, "anti-sense" refers to small, many times synthetic, oligonucleotides, resembling single-stranded DNA, targeted to a specific gene, its flanking regions, mRNA or protein encoded by the gene and mRNA, which may be utilized for inhibiting gene expression by inhibiting the function of the target messenger RNA (mRNA). Milligan, J. F. et al., J. Med. Chem. 36(14), 1923-1937 (1993). The present invention, thus, is intended for inhibiting gene expression of the adenosine  $A_1$ ,  $A_{2b}$  or  $A_3$  receptor as well as for promoting the gene expression of the adenosine  $A_{2a}$ receptor. As is generally known in the art, the inhibition of gene expression may be I brought about through anti-sense oligonucleotide hybridization to the coding (sense) sequences in a specific messenger RNA (mRNA) target, e.g. by hydrogen bonding according to Watson-Crick base pairing rules. In general, the exogenously administered anti-sense oligos decrease the mRNA and protein levels of the target gene or cause changes in the growth characteristics or shapes of the cells. Ibid. See, also Helene, C. and Toulme, J., Biochim. Biophys. Acta 1049: 99-125 (1990); Cohen, J. S., Ed., Oligodeoxynucleotides as Anti-sense Inhibitors of Gene Expression; CRC Press: Boca Raton, FL (1987). As used herein, "adenosine receptor anti-sense oligonucleotide (oligo)" is a short sequence of synthetic nucleotide that (1) hybridizes to any coding sequence in an mRNA which codes for an adenosine receptor, e.g., the adenosine A₁, A_{2b} or A₃ receptor, under in vivo hybridization conditions described below, and that (2) upon hybridization causes a decrease in gene expression of the adenosine A₁, A_{2b} or A₃ receptor. As used in this patent an adenosine A_{2a} agonist is any compound or agent that triggers an A_{2a} mediated agonist response or increases the level of A_{2a} receptor. As used in this patent, an adenosine A_{2a} agonist is any compound or agent that triggers an A2a mediated agonist response or increases the level of A_{2a} receptor.

The mRNA sequence of the adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  and  $A_3$  receptors may be derived from the DNA base sequences of the genes expressing either the adenosine  $A_1$ ,  $A_{2b}$  and  $A_3$  receptors. The sequence of the genomic human adenosine  $A_1$  receptor is known and is disclosed in U.S. Patent No. 5,320,962 to G. Stiles et al. The adenosine  $A_{2b}$  receptor is also known. See, for example, GenBank, Accession No. X68486; GenBank Accession No. X68487. The adenosine  $A_3$  receptor has been cloned, sequenced and expressed in rat and humans. See, F. Zhou et al., Proc. Nat'1. Acad. Sci. (USA) 89:7432 (1992); M.A. Jacobson et al., U.K. Patent Application No. 9304582.1 (1993). The anti-sense oligonucleotides that down-regulate the production of the adenosine  $A_1$ ,  $A_{2b}$  and  $A_3$  receptor and to upregulate the adenosine  $A_{2a}$  receptor may be produced in accordance with standard techniques. Adenosine  $A_{2a}$  agonists are known in the art and need not be listed here.

The agent of this invention binds specifically with any sequence of a mRNA molecule which is

associated with or encodes an adenosine  $A_1$ ,  $A_{2a}$ ,  $A_{2b}$  or  $A_3$  receptor, and prevents translation of the mRNA molecule. In one embodiment of the present invention, the anti-sense oligonucleotide has one of the following sequences. In another preferred embodiment, the agent of the invention comprises fragments of these sequences or their combinations as well as sequences with decreased adenosine contents when compared with the natural sequences, where one or more adenosines are replaced by a universal base or adenosine analogue which does not activate adenosine receptors, particularly adenosine  $A_1$  receptors.

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5'-GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)
5'-GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3)
5'-GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5)
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In still another embodiment, oligos that are anti-sense to the adenosine  $A_{2a}$  receptor and have agonistic activity and other adenosine  $A_{2a}$  receptor agents are used for the treatment of RDS and other respiratory problems in "preemies."

In another embodiment of the invention, the sequence of the anti-sense oligonucleotide brackets the initiation codon of the adenosine  $A_1$  receptor, for example that of the human receptor mRNA. Preferred human adenosine  $A_1$  receptor anti-sense oligonucleotide may have the SEQ. ID NO: 7 or any one of its fragments, including one of the following sequences. In another preferred embodiment, fragments of these sequences and/or their combinations are also within the confines of the invention.

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5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(SEQ. ID NO:7) ,
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'(Fragment 1) (SEQ. ID NO:8) 5'-GGC GGC
CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 2) (SEQ. ID NO:9)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'(Fragment 3) (SEQ. ID NO:10) 5'-GGC GGC
CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 4) (SEQ. ID NO:11)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 5) (SEQ. ID NO:12)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 6) (SEQ. ID NO:13)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 7) (SEQ. ID NO:14)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 8) (SEQ. ID NO:15)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 9) (SEQ. ID NO:16)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 10) (SEQ. ID NO:17) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 11) (SEQ. ID NO:18)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 12) (SEQ. ID NO:19)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 13) (SEQ. ID NO:20)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 14) (SEQ. ID NO:21)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 15) (SEQ. ID NO:22)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 16) (SEQ. ID NO:23) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 17) (SEQ. ID NO:24)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 18) (SEQ. ID NO:25)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 19) (SEQ. ID NO:26) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 20) (SEQ. ID NO:27)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 21) (SEQ. ID NO:28)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 22) (SEQ. ID NO:29) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 23) (SEQ. ID NO:30)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 24) (SEQ. ID NO:31)
5'-GGC GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 25) (SEQ. ID NO:32) 5'-GGC GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 26) (SEQ. ID NO:33)
5'-GGC GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 27) (SEQ. ID NO:34)
5'-GGC GGC CTG GAA AGC TGA GAT GG -3' (Fragment 28) (SEQ. ID NO:35) 5'-GGC GGC CTG GAA AGC TGA GAT G -3' (Fragment 29) (SEQ. ID NO:36)
5'-GGC GGC CTG GAA AGC TGA GAT -3' (Fragment 30) (SEQ. ID NO:37)
5'-GGC GGC CTG GAA AGC TGA GA-3' (Fragment 31) (SEQ. ID NO:38) 5'-GGC GGC CTG GAA AGC TGA G-3' (Fragment 32) (SEQ. ID NO:39)
5'-GGC GGC CTG GAA AGC TGA-3' (Fragment 33) (SEQ. ID NO:40)
5'-GGC GGC CTG GAA AGC TG-3' (Fragment 34) (SEQ. ID NO:41)
5'-GGC GGC CTG GAA AGC T-3' (Fragment 35) (SEQ. ID NO:42)
5'-GGC GGC CTG GAA AGC-3' (Fragment 36) (SEQ. ID NO:43)
5'-GGC GGC CTG GAA AG-3' (Fragment 37) (SEQ. ID NO:44)
5'-GGC GGC CTG GAA A-3' (Fragment 38) (SEQ. ID NO:45)
5'-GGC GGC CTG GAA-3' (Fragment 39) (SEQ. ID NO:46)
5'-GGC GGC CTG GA-3' (Fragment 40) (SEQ. ID NO:47)
5'-GGC GGC CTG G-3' (Fragment 41) (SEQ. ID NO:48)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
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(Fragment 42) (SEQ. ID NO:49)
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
 (Fragment 43) (SEQ. ID NO:50)
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
 (Fragment 44) (SEQ. ID NO:51)
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'
 (Fragment 45) (SEQ. ID NO:52)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 46) (SEQ. ID NO:53) 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 47) (SEQ. ID NO:54)
 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 48) (SEQ. ID NO:55)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 49) (SEQ. ID NO:56) 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 50) (SEQ. ID NO:57)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 51) (SEQ. ID NO:58)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 52) (SEQ. ID NO:59)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 53) (SEQ. ID NO:60)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 54) (SEQ. ID NO:61)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 55) (SEQ. ID NO:62)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 56) (SEO. ID NO:63)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 57) (SEQ. ID NO:64)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 58) (SEQ. ID NO:65)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 59) (SEQ. ID NO:66)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 60) (SEQ. ID NO:67)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 61) (SEQ. ID NO:68)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 62) (SEQ. ID NO:69)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 63) (SEQ. ID NO:70) 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 64) (SEQ. ID NO:71)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 65) (SEQ. ID NO:72)
5'-GC GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 66) (SEQ. ID NO:73)
5'-GC GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 67) (SEQ. ID NO:74)
5'-GC GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 68) (SEQ. ID NO:75) 5'-GC GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 69) (SEQ. ID NO:76)
5'-GC GGC CTG GAA AGC TGA GAT GG -3' (Fragment 70) (SEQ. ID NO:77)
5'-GC GGC CTG GAA AGC TGA GAT G -3' (Fragment 71) (SEQ. ID NO:78) 5'-GC GGC CTG GAA AGC TGA GAT -3' (Fragment 72) (SEQ. ID NO:79)
5'-GC GGC CTG GAA AGC TGA GA-3' (Fragment 73) (SEQ. ID NO:80)
5'-GC GGC CTG GAA AGC TGA G-3' (Fragment 74) (SEQ. ID NO:81)
5'-GC GGC CTG GAA AGC TGA-3' (Fragment 75) (SEQ. ID NO:82)
5'-GC GGC CTG GAA AGC TG-3' (Fragment 76) (SEQ. ID NO:83)
5'-GC GGC CTG GAA AGC T-3' (Fragment 77) (SEQ. ID NO:84) 5'-GC GGC CTG GAA AGC-3' (Fragment 78) (SEQ. ID NO:85)
5'-GC GGC CTG GAA AG-3' (Fragment 79) (SEQ. ID NO:86)
5'-GC GGC CTG GAA A-3' (Fragment 80) (SEQ. ID NO:87)
5'-GC GGC CTG GAA-3' (Fragment 81) (SEQ. ID NO:88)
5'-GC GGC CTG GA-3' (Fragment 82) (SEQ. ID NO:89)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
(Fragment 83) (SEQ. ID NO:90)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3
'(Fragment 84) (SEQ. ID NO:91)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
(Fragment 85) (SEQ. ID NO:92)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3'(Fragment 86) (SEQ. ID NO:93)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 87) (SEO. ID NO:94)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 88) (SEQ. ID NO:95)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 89) (SEQ. ID NO:96)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 90) (SEQ. ID NO:97)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 91) (SEQ. ID NO:98)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 92) (SEQ. ID NO:99)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 93) (SEQ. ID NO:100)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 94) (SEO. 1D NO:101)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 95) (SEQ. ID NO:102)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 96) (SEQ. ID NO:103)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 97) (SEQ. ID NO:104)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 98) (SEQ. ID NO:105)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 99) (SEQ. ID NO:106)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 100) (SEQ. ID NO:107)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 101) (SEQ. ID NO:108)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 102) (SEQ. ID NO:109)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 103) (SEQ. ID NO:110)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 104) (SEQ. ID NO:111)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 105) (SEQ. ID NO:112)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 106) (SEQ. ID NO:113)
5'-C GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 107) (SEQ. ID NO:114)
5'-C GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 108) (SEQ. ID NO:115)
5'-C GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 109) (SEQ. ID NO:116)
5'-C GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 110) (SEQ. ID NO:117)
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5'-C GGC CTG GAA AGC TGA GAT GG -3' (Fragment 111) (SEQ. ID NO:118)
  5'-C GGC CTG GAA AGC TGA GAT G -3' (Fragment 112) (SEQ. ID NO:119)
  5'-C GGC CTG GAA AGC TGA GAT -3' (Fragment 113) (SEQ. ID NO:120)
  5'-C GGC CTG GAA AGC TGA GA-3' (Fragment 114) (SEQ. ID NO:121)
  5'-C GGC CTG GAA AGC TGA G-3' (Fragment 115) (SEO. ID NO:122)
  5'-C GGC CTG GAA AGC TGA-3' (Fragment 116) (SEQ. ID NO:123)
5'-C GGC CTG GAA AGC TG-3' (Fragment 117) (SEQ. ID NO:124)
  5'-C GGC CTG GAA AGC T-3' (Fragment 118) (SEQ. ID NO:125)
  5'-C GGC CTG GAA AGC-3' (Fragment 119) (SEQ. ID NO:126)
  5'-C GGC CTG GAA AG-3' (Fragment 120) (SEQ. ID NO:127)
  5'-C GGC CTG GAA A-3' (Fragment 121) (SEQ. ID NO:128)
  5'-C GGC CTG GAA-3' (Fragment 122) (SEQ. ID NO:129)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
  (Fragment 123) (SEQ. ID NO:130)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
  (Fragment 124) (SEQ. ID NO:131)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3'
  (Fragment 125) (SEQ. ID NO:132)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3 (Fragment 126) (SEQ. ID NO:133)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 127) (SEQ. ID NO:134)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 128) (SEQ. ID NO:135)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 129) (SEQ. ID NO:136)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 130) (SEQ. ID NO:137)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 131) (SEQ. ID NO:138)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 132) (SEQ. ID NO:139)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3'(Fragment 133) (SEQ. ID NO:140)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 134) (SEQ. ID NO:141)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 135) (SEQ. ID NO:142)
  5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 136) (SEQ. ID NO:143)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 137) (SEQ. ID NO:144)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 138) (SEQ. ID NO:145)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 139) (SEQ. ID NO:146)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT G-3' (Fragment 140) (SEQ. ID NO:147)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 141) (SEQ. ID NO:148)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 142) (SEQ. ID NO:149)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 143) (SEQ. ID NO:150)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 144) (SEQ. ID NO:151)
5'- GGC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 145) (SEQ. ID NO:152)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 146) (SEQ. ID NO:153)
 5'- GGC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 147) (SEQ. ID NO:154)
 5'- GGC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 148) (SEQ. ID NO:155)
 5'- GGC CTG GAA AGC TGA GAT GGA G -3' (Fragment 149) (SEQ. ID NO:156)
5'- GGC CTG GAA AGC TGA GAT GGA -3' (Fragment 150) (SEQ. ID NO:157)
5'- GGC CTG GAA AGC TGA GAT GG -3' (Fragment 151) (SEQ. ID NO:158)
 5'- GGC CTG GAA AGC TGA GAT G -3' (Fragment 152) (SEQ. ID NO:159)
 5'- GGC CTG GAA AGC TGA GAT -3' (Fragment 153) (SEO. ID NO:160)
5'- GGC CTG GAA AGC TGA GA-3' (Fragment 154) (SEQ. ID NO:161)
5'- GGC CTG GAA AGC TGA G-3' (Fragment 155) (SEQ. ID NO:162)
5'- GGC CTG GAA AGC TGA-3' (Fragment 156) (SEQ. ID NO:163)
5'- GGC CTG GAA AGC TG-3' (Fragment 157) (SEO. ID NO:164)
5'- GGC CTG GAA AGC T-3' (Fragment 158) (SEQ. ID NO:165)
5'- GGC CTG GAA AGC-3' (Fragment 159) (SEQ. ID NO:166)
5'- GGC CTG GAA AG-3' (Fragment 160) (SEQ. ID NO:167)
5'- GGC CTG GAA A-3' (Fragment 161) (SEQ. ID NO:168)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'
 (Fragment 162) (SEQ. ID NO:169)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'
(Fragment 163) (SEQ. ID NO:170)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 164) (SEQ. ID NO:171) 5'- GC CTG
GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 165) (SEQ. ID NO:172)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 166) (SEQ. ID NO:173)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 167) (SEQ. ID NO:174)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 168) (SEQ. ID NO:175)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 169) (SEQ. ID NO:176)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 170) (SEQ. ID NO:177)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 171) (SEQ. ID NO:178)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 172) (SEQ. 1D NO:179)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 173) (SEQ. ID NO:180)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 174) (SEQ. ID NO:181)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 175) (SEQ. ID NO:182)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 176) (SEQ. ID NO:183)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 177) (SEQ. ID NO:184)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 178) (SEQ. ID NO:185)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 179) (SEQ. ID NO:186)
5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 180) (SEQ. ID NO:187)
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27 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 181) (SEQ. ID NO:188) 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 182) (SEQ. ID NO:189) 5'- GC CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 183) (SEQ. ID NO:190) 5'- GC CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 184) (SEQ. ID NO:191) 5'- GC CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 185) (SEQ. ID NO:192) 5'- GC CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 186) (SEQ. ID NO:193) 5'- GC CTG GAA AGC TGA GAT GGA GG -3' (Fragment 187) (SEQ. ID NO:194) 5'- GC CTG GAA AGC TGA GAT GGA G -3' (Fragment 188) (SEQ. ID NO:195) 5'- GC CTG GAA AGC TGA GAT GGA -3' (Fragment 189) (SEQ. ID NO:196) 5'- GC CTG GAA AGC TGA GAT GG -3' (Fragment 190) (SEQ. ID NO:197) 5'- GC CTG GAA AGC TGA GAT G -3' (Fragment 191) (SEQ. ID NO:198) 5'- GC CTG GAA AGC TGA GAT -3' (Fragment 192) (SEQ. ID NO:199) 5'- GC CTG GAA AGC TGA GA-3' (Fragment 193) (SEQ. ID NO:200) 5'- GC CTG GAA AGC TGA G-3' (Fragment 194) (SEQ. ID NO:201) 5'- GC CTG GAA AGC TGA-3' (Fragment 195) (SEQ. ID NO:202) 5'- GC CTG GAA AGC TG-3' (Fragment 196) (SEQ. ID NO:203) 5'- GC CTG GAA AGC T-3' (Fragment 197) (SEQ. ID NO:204) 5'- GC CTG GAA AGC-3' (Fragment 198) (SEQ. ID NO:205) 5'- GC CTG GAA AG-3' (Fragment 199) (SEQ. ID NO:206) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 200) (SEO. ID NO:207) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 201) (SEQ. ID NO:208)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 202) (SEQ. ID NO:209) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 203) (SEO. ID NO:210) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3'(Fragment 204) (SEQ. ID NO:211)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 205) (SEQ. ID NO:212) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 206) (SEQ. ID NO:213) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 207) (SEQ. ID NO:214)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 208) (SEQ. ID NO:215) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 209) (SEQ. ID NO:216) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 210) (SEQ. ID NO:217)
5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 211) (SEQ. ID NO:218) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 212) (SEQ. ID NO:219) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 213) (SEQ. ID NO:220) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 214) (SEQ. ID NO:221) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 215) (SEQ. ID NO:222) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 216) (SEQ. ID NO:223) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 217) (SEQ. ID NO:224) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 218) (SEQ. ID NO:225) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 219) (SEQ. ID NO:226) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 220) (SEQ. ID NO:227) 5'- C CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 221) (SEQ. ID NO:228) 5'- C CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 222) (SEQ. ID NO:229) 5'- C CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 223) (SEQ. ID NO:230) 5'- C CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 224) (SEQ. ID NO:231) 5'- C CTG GAA AGC TGA GAT GGA GG -3' (Fragment 225) (SEQ. ID NO:232) 5'- C CTG GAA AGC TGA GAT GGA G -3' (Fragment 226) (SEQ. ID NO:233) 5'- C CTG GAA AGC TGA GAT GGA -3' (Fragment 227) (SEQ. ID NO:234) 5'- C CTG GAA AGC TGA GAT GG -3' (Fragment 228) (SEQ. ID NO:235) 5'- C CTG GAA AGC TGA GAT G -3' (Fragment 229) (SEQ. ID NO:236) 5'- C CTG GAA AGC TGA GAT -3' (Fragment 230) (SEQ. ID NO:237) 5'- C CTG GAA AGC TGA GA-3' (Fragment 231) (SEQ. ID NO:238) 5'- C CTG GAA AGC TGA G-3' (Fragment 232) (SEQ. ID NO:239) 5'- C CTG GAA AGC TGA-3' (Fragment 233) (SEQ. ID NO:240) 5'- C CTG GAA AGC TG-3' (Fragment 234) (SEQ. ID NO:241) 5'- C CTG GAA AGC T-3' (Fragment 235) (SEQ. ID NO:242) 5'- C CTG GAA AGC-3' (Fragment 236) (SEQ. ID NO:243) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 237) (SEQ. ID NO:244) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 238) (SEQ. ID NO:245)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 239) (SEQ. ID NO:246) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 240) (SEQ. ID NO:247)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 241) (SEQ. ID NO:248) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 242) (SEQ. ID NO:249) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 243) (SEQ. ID NO:250)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 244) (SEQ. ID NO:251) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 245) (SEO. ID NO:252) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 246) (SEQ. ID NO:253)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 247) (SEQ. ID NO:254) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 248) (SEO. 1D NO:255) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 249) (SEQ. ID NO:256)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 250) (SEQ. ID NO:257)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 251) (SEQ. ID NO:258) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 252) (SEQ. ID NO:259)
5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 253) (SEQ. ID NO:260) 5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 254) (SEQ. ID NO:261)

5'- CTG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 255) (SEQ. ID NO:262)

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5'- CTG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 256) (SEQ. ID NO:263)
5'- CTG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 257) (SEQ. ID NO:264)
5'- CTG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 258) (SEQ. ID NO:265) 5'- CTG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 259) (SEQ. ID NO:266)
5'- CTG GAA AGC TGA GAT GGA GGG C -3' (Fragment 260) (SEQ. ID NO:267)
5'- CTG GAA AGC TGA GAT GGA GGG -3' (Fragment 261) (SEQ. ID NO:268)
5'- CTG GAA AGC TGA GAT GGA GG -3' (Fragment 262) (SEQ. ID NO:269)
5'- CTG GAA AGC TGA GAT GGA G -3' (Fragment 263) (SEQ. ID NO:270)
5'- CTG GAA AGC TGA GAT GGA -3' (Fragment 264) (SEQ. ID NO:271)
5'- CTG GAA AGC TGA GAT GG -3' (Fragment 265) (SEQ. ID NO:272)
5'- CTG GAA AGC TGA GAT G -3' (Fragment 266) (SEQ. ID NO:273)
5'- CTG GAA AGC TGA GAT -3' (Fragment 267) (SEQ. ID NO:274)
5'- CTG GAA AGC TGA GA-3' (Fragment 268) (SEQ. ID NO:275)
5'- CTG GAA AGC TGA G-3' (Fragment 269) (SEQ. ID NO:276)
5'- CTG GAA AGC TGA-3' (Fragment 270) (SEQ. ID NO:277)
5'- CTG GAA AGC TG-3' (Fragment 271) (SEQ. ID NO:278)
5'- CTG GAA AGC T-3' (Fragment 272) (SEQ. ID NO:279)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 273) (SEQ. ID NO:280)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 274) (SEQ. ID NO:281)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 275) (SEO, ID NO:282)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 276) (SEQ. ID NO:283)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 277) (SEQ. ID NO:284)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 278) (SEQ. ID NO:285)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 279) (SEQ. ID NO:286)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 280) (SEQ. ID NO:287)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 281) (SEQ. ID NO:288)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 282) (SEQ. ID NO:289)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 283) (SEQ. ID NO:290)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 284) (SEQ. ID NO:291)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 285) (SEQ. ID NO:292)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 286) (SEQ. ID NO:293)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 287) (SEQ. ID NO:294)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 288) (SEQ. ID NO:295)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 289) (SEQ. ID NO:296)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT G-3' (Fragment 290) (SEQ. ID NO:297)
5'- TG GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 291) (SEQ. ID NO:298)
5'- TG GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 292) (SEQ. ID NO:299)
5'- TG GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 293) (SEQ. ID NO:300)
5'- TG GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 294) (SEQ. ID NO:301)
5'- TG GAA AGC TGA GAT GGA GGG CG -3' (Fragment 295) (SEQ. ID NO:302)
5'- TG GAA AGC TGA GAT GGA GGG C -3' (Fragment 296) (SEQ. ID NO:303)
5'- TG GAA AGC TGA GAT GGA GGG -3' (Fragment 297) (SEQ. ID NO:304)
5'- TG GAA AGC TGA GAT GGA GG -3' (Fragment 298) (SEQ. ID NO:305)
5'- TG GAA AGC TGA GAT GGA G -3' (Fragment 299) (SEQ. ID NO:306)
5'- TG GAA AGC TGA GAT GGA -3' (Fragment 300) (SEQ. ID NO:307)
5'- TG GAA AGC TGA GAT GG -3' (Fragment 301) (SEQ. ID NO:308)
5'- TG GAA AGC TGA GAT G -3' (Fragment 302) (SEQ. ID NO:309)
5'- TG GAA AGC TGA GAT -3' (Fragment 303) (SEQ. ID NO:310)
5'- TG GAA AGC TGA GA-3' (Fragment 304) (SEQ. ID NO:311)
5'- TG GAA AGC TGA G-3' (Fragment 305) (SEQ. ID NO:312)
5'- TG GAA AGC TGA-3' (Fragment 306) (SEQ. ID NO:313)
5'- TG GAA AGC TG-3' (Fragment 307) (SEQ. ID NO:314)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 308) (SEO. ID NO:315)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3'(Fragment 309) (SEQ. ID NO:316)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 310) (SEQ. ID NO:317)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 311) (SEO. ID NO:318)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 312) (SEQ. ID NO:319)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 313) (SEQ. ID NO:320)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 314) (SEQ. ID NO:321)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 315) (SEQ. ID NO:322) 5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 316) (SEQ. ID NO:323)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 317) (SEQ. ID NO:324)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 318) (SEQ. ID NO:325)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 319) (SEQ. ID NO:326)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 320) (SEQ. ID NO:327)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC GG -3' (Fragment 321) (SEQ. ID NO:328)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 322) (SEQ. ID NO:329)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GGC -3 (Fragment 323) (SEQ. ID NO:330)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 324) (SEQ. ID NO:331)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT G-3' (Fragment 325) (SEQ. ID NO:332)
5'- G GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 326) (SEO. ID NO:333)
5'- G GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 327) (SEQ. ID NO:334)
5'- G GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 328) (SEQ. ID NO:335)
5'- G GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 329) (SEQ. ID NO:336)
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5'- G GAA AGC TGA GAT GGA GGG CG -3' (Fragment 330) (SEQ. ID NO:337)

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5'- G GAA AGC TGA GAT GGA GGG C -3' (Fragment 331) (SEQ. ID NO:338)
5'- G GAA AGC TGA GAT GGA GGG -3' (Fragment 332) (SEQ. ID NO:339)
5'- G GAA AGC TGA GAT GGA GG -3' (Fragment 333) (SEQ. ID NO:340)
5'- G GAA AGC TGA GAT GGA G -3' (Fragment 334) (SEQ. ID NO:341)
5'- G GAA AGC TGA GAT GGA -3' (Fragment 335) (SEQ. ID NO:342)
5'- G GAA AGC TGA GAT GG -3' (Fragment 336) (SEQ. ID NO:343)
5'- G GAA AGC TGA GAT G -3' (Fragment 337) (SEQ. ID NO:344)
5'- G GAA AGC TGA GAT -3' (Fragment 338) (SEQ. ID NO:345)
5'- G GAA AGC TGA GA-3' (Fragment 339) (SEQ. ID NO:346)
5'- G GAA AGC TGA G-3' (Fragment 340) (SEQ. ID NO:347)
5'- G GAA AGC TGA-3' (Fragment 341) (SEQ. ID NO:348)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 342) (SEQ. ID NO:349)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 343) (SEQ. ID NO:350)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 344) (SEQ. ID NO:351)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 345) (SEQ. ID NO:352)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 346) (SEQ. ID NO:353)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 347) (SEQ. ID NO:354)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 348) (SEQ. ID NO:355)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 349) (SEQ. ID NO:356)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 350) (SEQ. ID NO:357)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 351) (SEQ. ID NO:358)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 352) (SEO. ID NO:359)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 353) (SEQ. ID NO:360)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 354) (SEQ. ID NO:361)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 355) (SEQ. ID NO:362)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 356) (SEQ. ID NO:363)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 357) (SEQ. ID NO:364)
5'- GAA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 358) (SEQ. ID NO:365)
5'- GAA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 359) (SEQ. ID NO:366)
5'- GAA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 360) (SEQ. ID NO:367)
5'- GAA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 361) (SEQ. ID NO:368)
5'- GAA AGC TGA GAT GGA GGG CGG C-3' (Fragment 362) (SEQ. ID NO:369)
5'- GAA AGC TGA GAT GGA GGG CGG -3' (Fragment 363) (SEQ. ID NO:370)
5'- GAA AGC TGA GAT GGA GGG CG -3' (Fragment 364) (SEQ. ID NO:371)
5'- GAA AGC TGA GAT GGA GGG C -3' (Fragment 365) (SEQ. ID NO:372)
5'- GAA AGC TGA GAT GGA GGG -3' (Fragment 366) (SEQ. ID NO:373)
5'- GAA AGC TGA GAT GGA GG -3' (Fragment 367) (SEQ. ID NO:374)
5'- GAA AGC TGA GAT GGA G -3' (Fragment 368) (SEQ. ID NO:375)
5'- GAA AGC TGA GAT GGA -3' (Fragment 369) (SEQ. ID NO:376)
5'- GAA AGC TGA GAT GG -3' (Fragment 370) (SEQ. ID NO:377)
5'- GAA AGC TGA GAT G -3' (Fragment 371) (SEQ. ID NO:378)
5'- GAA AGC TGA GAT -3' (Fragment 372) (SEQ. ID NO:379)
5'- GAA AGC TGA GA-3' (Fragment 373) (SEQ. ID NO:380)
5'- GAA AGC TGA G-3' (Fragment 374) (SEQ. ID NO:381)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 375) (SEQ. ID NO:382)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 376) (SEQ. ID NO:383)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 377) (SEQ. ID NO:384)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 378) (SEQ. ID NO:385)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 379) (SEQ. ID NO:386)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 380) (SEQ. ID NO:387)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 381) (SEQ. ID NO:388)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 382) (SEQ. ID NO:389)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 383) (SEQ. ID NO:390)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 384) (SEQ. ID NO:391)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 385) (SEQ. ID NO:392)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 386) (SEQ. ID NO:393)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 387) (SEQ. ID NO:394)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 388) (SEQ. ID NO:395)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 389) (SEQ. ID NO:396)
5'- AA AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 390) (SEQ. ID NO:397)
5'- AA AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 391) (SEQ. ID NO:398)
5'- AA AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 392) (SEQ. ID NO:399)
5'- AA AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 393) (SEQ. ID NO:400)
5'- AA AGC TGA GAT GGA GGG CGG CA-3' (Fragment 394) (SEQ. ID NO:401)
5'- AA AGC TGA GAT GGA GGG CGG C-3' (Fragment 395) (SEQ. ID NO:402)
5'- AA AGC TGA GAT GGA GGG CGG -3' (Fragment 396) (SEQ. ID NO:403)
5'- AA AGC TGA GAT GGA GGG CG -3' (Fragment 397) (SEQ. ID NO:404)
5'- AA AGC TGA GAT GGA GGG C -3' (Fragment 398) (SEQ. ID NO:405)
5'- AA AGC TGA GAT GGA GGG -3' (Fragment 399) (SEQ. ID NO:406)
5'- AA AGC TGA GAT GGA GG -3' (Fragment 400) (SEQ. ID NO:407)
5'- AA AGC TGA GAT GGA G -3' (Fragment 401) (SEQ. ID NO:408)
5'- AA AGC TGA GAT GGA -3' (Fragment 402) (SEQ. ID NO:409)
5'- AA AGC TGA GAT GG -3' (Fragment 403) (SEQ. ID NO:410)
5'- AA AGC TGA GAT G -3' (Fragment 404) (SEQ. ID NO:411)
5'- AA AGC TGA GAT -3' (Fragment 405) (SEQ. ID NO:412)
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5'- AA AGC TGA GA-3' (Fragment 406) (SEQ. ID NO:413) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 407) (SEQ. ID NO:414) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 408) (SEQ. ID NO:415) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 409) (SEQ. ID NO:416) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 410) (SEQ. ID NO:417)
5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 411) (SEQ. ID NO:418) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 412) (SEO. ID NO:419) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 413) (SEQ. ID NO:420) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 414) (SEQ. ID NO:421) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 415) (SEQ. ID NO:422) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 416) (SEQ. ID NO:423) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 417) (SEQ. ID NO:424) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 418) (SEQ. ID NO:425) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 419) (SEQ. ID NO:426) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 420) (SEQ. ID NO:427) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 421) (SEQ. ID NO:428) 5'- A AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 422) (SEQ. ID NO:429) 5'- A AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 423) (SEQ. ID NO:430) 5'- A AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 424) (SEQ. ID NO:431) 5'- A AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 425) (SEQ. ID NO:432) 5'- A AGC TGA GAT GGA GGG CGG CA-3' (Fragment 426) (SEQ. ID NO:433) 5'- A AGC TGA GAT GGA GGG CGG C-3' (Fragment 427) (SEQ. ID NO:434) 5'- A AGC TGA GAT GGA GGG CGG -3' (Fragment 428) (SEQ. ID NO:435) 5'- A AGC TGA GAT GGA GGG CG -3' (Fragment 429) (SEQ. ID NO:436) 5'- A AGC TGA GAT GGA GGG C -3' (Fragment 430) (SEQ. ID NO:437) 5'- A AGC TGA GAT GGA GGG -3' (Fragment 431) (SEQ. ID NO:438) 5'- A AGC TGA GAT GGA GG -3' (Fragment 432) (SEQ. ID NO:439) 5'- A AGC TGA GAT GGA G -3' (Fragment 433) (SEQ. ID NO:440) 5'- A AGC TGA GAT GGA -3' (Fragment 434) (SEQ. ID NO:441) 5'- A AGC TGA GAT GG -3' (Fragment 435) (SEQ. ID NO:442) 5'- A AGC TGA GAT G -3' (Fragment 436) (SEQ. ID NO:443) 5'- A AGC TGA GAT -3' (Fragment 437) (SEQ. ID NO:444) 5'- AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 438) (SEQ. ID NO:445) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 439) (SEQ. ID NO:446) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 440) (SEQ. ID NO:447) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 441) (SEQ. ID NO:448) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 442) (SEO, ID NO:449) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 443) (SEQ. ID NO:450) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 444) (SEQ. ID NO:451) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 445) (SEQ. ID NO:452) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 446) (SEQ. ID NO:453) AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 447) (SEQ. ID NO:454) AGC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 448) (SEQ. ID NO:455) AGC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 449) (SEQ. ID NO:456) AGC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 450) (SEQ. ID NO:457) AGC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 451) (SEQ. ID NO:458) AGC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 452) (SEQ. ID NO:459) AGC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 453) (SEQ. ID NO:460) AGC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 454) (SEQ. ID NO:461) AGC TGA GAT GGA GGG CGG CAT G -3' (Fragment 455) (SEQ. ID NO:462) AGC TGA GAT GGA GGG CGG CAT -3' (Fragment 456) (SEQ. ID NO:463) AGC TGA GAT GGA GGG CGG CA-3' (Fragment 457) (SEO. ID NO:464) AGC TGA GAT GGA GGG CGG C-3' (Fragment 458) (SEQ. ID NO:465) AGC TGA GAT GGA GGG CGG -3' (Fragment 459) (SEQ. ID NO:466) AGC TGA GAT GGA GGG CG -3' (Fragment 460) (SEQ. ID NO:467) AGC TGA GAT GGA GGG C -3' (Fragment 461) (SEQ. ID NO:468) AGC TGA GAT GGA GGG -3' (Fragment 462) (SEQ. ID NO:469) AGC TGA GAT GGA GG -3' (Fragment 463) (SEQ. ID NO:470) AGC TGA GAT GGA G -3' (Fragment 464) (SEQ. ID NO:471) AGC TGA GAT GGA -3' (Fragment 465) (SEQ. ID NO:472) AGC TGA GAT GG -3' (Fragment 466) (SEQ. ID NO:473) AGC TGA GAT G -3' (Fragment 467) (SEQ. ID NO:474) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 468) (SEQ. ID NO:475) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 469) (SEQ. ID NO:476) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 470) (SEQ. ID NO:477) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 471) (SEQ. ID NO:478) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 472) (SEQ. ID NO:479) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 473) (SEQ. ID NO:480) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 474) (SEQ. ID NO:481) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 475) (SEQ. ID NO:482) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 476) (SEQ. ID NO:483) GC TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 477) (SEQ. ID NO:484) GC TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 478) (SEQ. ID NO:485) GC TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 479) (SEQ. ID NO:486) GC TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 480) (SEQ. ID NO:487)

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5'- GC TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 481) (SEQ. ID NO:488)
5'- GC TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 482) (SEQ. ID NO:489)
5'- GC TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 483) (SEQ. ID NO:490)
    GC TGA GAT GGA GGG CGG CAT GG -3' (Fragment 484) (SEQ. ID NO:491)
    GC TGA GAT GGA GGG CGG CAT G -3' (Fragment 485) (SEQ. ID NO:492) GC TGA GAT GGA GGG CGG CAT -3' (Fragment 486) (SEQ. ID NO:493)
    GC TGA GAT GGA GGG CGG CA-3' (Fragment 487) (SEQ. ID NO:494)
    GC TGA GAT GGA GGG CGG C-3' (Fragment 488) (SEQ. ID NO:495) GC TGA GAT GGA GGG CGG -3' (Fragment 489) (SEQ. ID NO:496)
    GC TGA GAT GGA GGG CG -3' (Fragment 490) (SEQ. ID NO:497)
    GC TGA GAT GGA GGG C -3' (Fragment 491) (SEQ. ID NO:498)
    GC TGA GAT GGA GGG -3' (Fragment 492) (SEQ. ID NO:499)
    GC TGA GAT GGA GG -3' (Fragment 493) (SEQ. ID NO:500)
    GC TGA GAT GGA G -3' (Fragment 494) (SEQ. ID NO:501)
GC TGA GAT GGA -3' (Fragment 495) (SEQ. ID NO:502)
    GC TGA GAT GG -3' (Fragment 496) (SEQ. ID NO:503)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 497) (SEQ. ID NO:504)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 498) (SEQ. ID NO:505)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 499) (SEQ. ID NO:506)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 500) (SEQ. ID NO:507) C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 501) (SEQ. ID NO:508)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 502) (SEQ. ID NO:509)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 503) (SEQ. ID NO:510) C TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 504) (SEQ. ID NO:511)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 505) (SEQ. ID NO:512)
    C TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 506) (SEQ. ID NO:513)
    C TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 507) (SEQ. ID NO:514)
    C TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 508) (SEQ. ID NO:515)
    C TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 509) (SEQ. ID NO:516)
    C TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 510) (SEQ. ID NO:517)
    C TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 511) (SEQ. ID NO:518)
    C TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 512) (SEQ. ID NO:519)
    C TGA GAT GGA GGG CGG CAT GG -3' (Fragment 513) (SEQ. ID NO:520)
    C TGA GAT GGA GGG CGG CAT G -3' (Fragment 514) (SEQ. ID NO:521)
    C TGA GAT GGA GGG CGG CAT -3' (Fragment 515) (SEQ. ID NO:522)
    C TGA GAT GGA GGG CGG CA-3' (Fragment 516) (SEQ. ID NO:523)
    C TGA GAT GGA GGG CGG C-3' (Fragment 517) (SEQ. ID NO:524)
    C TGA GAT GGA GGG CGG -3' (Fragment 518) (SEQ. ID NO:525)
    C TGA GAT GGA GGG CG -3' (Fragment 519) (SEQ. ID NO:526)
    C TGA GAT GGA GGG C -3' (Fragment 520) (SEQ. ID NO:527)
    C TGA GAT GGA GGG -3' (Fragment 521) (SEQ. ID NO:528)
C TGA GAT GGA GG -3' (Fragment 522) (SEQ. ID NO:529)
    C TGA GAT GGA G -3' (Fragment 523) (SEQ. ID NO:530)
    C TGA GAT GGA -3' (Fragment 524) (SEQ. ID NO:531)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 525) (SEQ. ID NO:532)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 526) (SEQ. ID NO:533)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 527) (SEQ. ID NO:534)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 528) (SEQ. ID NO:535)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 529) (SEQ. ID NO:536)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 530) (SEQ. ID NO:537) TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 531) (SEQ. ID NO:538)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 532) (SEQ. ID NO:539)
     TGA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 533) (SEQ. ID NO:540) TGA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 534) (SEQ. ID NO:541)
     TGA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 535) (SEQ. ID NO:542)
     TGA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 536) (SEQ. ID NO:543)
     TGA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 537) (SEQ. ID NO:544)
     TGA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 538) (SEQ. ID NO:545)
     TGA GAT GGA GGG CGG CAT GGC G-3' (Fragment 539) (SEQ. ID NO:546) TGA GAT GGA GGG CGG CAT GGC -3' (Fragment 540) (SEQ. ID NO:547)
     TGA GAT GGA GGG CGG CAT GG -3' (Fragment 541) (SEQ. ID NO:548)
     TGA GAT GGA GGG CGG CAT G -3' (Fragment 542) (SEQ. ID NO:549)
     TGA GAT GGA GGG CGG CAT -3' (Fragment 543) (SEQ. ID NO:550)
     TGA GAT GGA GGG CGG CA-3' (Fragment 544) (SEQ. ID NO:551)
     TGA GAT GGA GGG CGG C-3' (Fragment 545) (SEQ. ID NO:552)
5'-
5'-
     TGA GAT GGA GGG CGG -3' (Fragment 546) (SEQ. ID NO:553)
     TGA GAT GGA GGG CG -3' (Fragment 547) (SEQ. ID NO:554)
     TGA GAT GGA GGG C -3' (Fragment 548) (SEQ. ID NO:555)
5'-
5'-
     TGA GAT GGA GGG -3' (Fragment 549) (SEQ. ID NO:556)
     TGA GAT GGA GG -3' (Fragment 550) (SEQ. ID NO:557)
5'-
     TGA GAT GGA G -3' (Fragment 551) (SEQ. ID NO:558)
     GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 552) (SEQ. ID NO:559)
     GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 553) (SEQ. ID NO:560)
5'-
5'-
     GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 554) (SEQ. ID NO:561)
     GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 555) (SEQ. ID NO:562)
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GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 556) (SEQ. ID NO:563)
      GA GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 557) (SEQ. ID NO:564)
      GA GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 558) (SEQ. ID NO:565) GA GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 559) (SEQ. ID NO:566)
5'-
      GA GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 560) (SEQ. ID NO:567)
      GA GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 561) (SEQ. ID NO:568) GA GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 562) (SEQ. ID NO:569)
      GA GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 563) (SEQ. ID NO:570)
      GA GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 564) (SEQ. ID NO:571)
GA GAT GGA GGG CGG CAT GGC GG-3' (Fragment 565) (SEQ. ID NO:572)
5'-
      GA GAT GGA GGG CGG CAT GGC G-3' (Fragment 566) (SEQ. ID NO:573)
5'-
      GA GAT GGA GGG CGG CAT GGC -3' (Fragment 567) (SEQ. ID NO:574)
5'-
      GA GAT GGA GGG CGG CAT GG -3' (Fragment 568) (SEQ. ID NO:575)
      GA GAT GGA GGG CGG CAT G -3' (Fragment 569) (SEQ. ID NO:576)
      GA GAT GGA GGG CGG CAT -3' (Fragment 570) (SEQ. ID NO:577)
      GA GAT GGA GGG CGG CA-3' (Fragment 571) (SEQ. ID NO:578)
5'-
      GA GAT GGA GGG CGG C-3' (Fragment 572) (SEQ. ID NO:579)
      GA GAT GGA GGG CGG -3' (Fragment 573) (SEQ. ID NO:580)
5'-
      GA GAT GGA GGG CG -3' (Fragment 574) (SEQ. ID NO:581)
      GA GAT GGA GGG C -3' (Fragment 575) (SEQ. ID NO:582)
      GA GAT GGA GGG -3' (Fragment 576) (SEQ. ID NO:583)
5'-
      GA GAT GGA GG -3' (Fragment 577) (SEQ. ID NO:584)
      A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 578) (SEO, ID NO:585)
5'-
      A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 579) (SEQ. ID NO:586) A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 580) (SEQ. ID NO:587)
5'-
      A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 581) (SEQ. ID NO:588)
      A GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 582) (SEQ. ID NO:589) A GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 583) (SEQ. ID NO:590)
5'-
5'-
      A GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 584) (SEQ. ID NO:591)
      A GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 585) (SEQ. ID NO:592)
A GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 586) (SEQ. ID NO:593)
5'-
      A GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 587) (SEQ. ID NO:594)
     A GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 588) (SEQ. ID NO:595)
A GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 589) (SEQ. ID NO:596)
5'-
      A GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 590) (SEQ. ID NO:597)
      A GAT GGA GGG CGG CAT GGC GG-3' (Fragment 591) (SEQ. ID NO:598)
      A GAT GGA GGG CGG CAT GGC G-3' (Fragment 592) (SEQ. ID NO:599)
5'-
      A GAT GGA GGG CGG CAT GGC -3' (Fragment 593) (SEQ. ID NO:600)
     A GAT GGA GGG CGG CAT GG -3' (Fragment 594) (SEQ. ID NO:601)
A GAT GGA GGG CGG CAT G -3' (Fragment 595) (SEQ. ID NO:602)
5'-
      A GAT GGA GGG CGG CAT -3' (Fragment 596) (SEQ. ID NO:603)
      A GAT GGA GGG CGG CA-3' (Fragment 597) (SEQ. ID NO:604)
5'-
      A GAT GGA GGG CGG C-3' (Fragment 598) (SEQ. ID NO:605)
      A GAT GGA GGG CGG -3' (Fragment 599) (SEQ. ID NO:606)
      A GAT GGA GGG CG -3' (Fragment 600) (SEQ. ID NO:607)
5'-
      A GAT GGA GGG C -3' (Fragment 601) (SEQ. ID NO:608)
      A GAT GGA GGG -3' (Fragment 602) (SEQ. ID NO:609)
      GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 603) (SEQ. ID NO:610) GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 604) (SEQ. ID NO:611)
5'-
      GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 605) (SEQ. ID NO:612)
      GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 606) (SEQ. ID NO:613) GAT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 607) (SEQ. ID NO:614)
5'-
      GAT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 608) (SEQ. ID NO:615)
      GAT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 609) (SEQ. ID NO:616) GAT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 610) (SEQ. ID NO:617)
5'-
      GAT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 611) (SEQ. ID NO:618)
      GAT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 612) (SEQ. ID NO:619) GAT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 613) (SEQ. ID NO:620)
5'-
5'-
      GAT GGA GGG CGG CAT GGC GGG C-3' (Fragment 614) (SEQ. ID NO:621)
      GAT GGA GGG CGG CAT GGC GGG -3' (Fragment 615) (SEQ. ID NO:622) GAT GGA GGG CGG CAT GGC GG-3' (Fragment 616) (SEQ. ID NO:623)
5'-
5'-
      GAT GGA GGG CGG CAT GGC G-3' (Fragment 617) (SEQ. ID NO:624)
      GAT GGA GGG CGG CAT GGC -3' (Fragment 618) (SEQ. ID NO:625)
      GAT GGA GGG CGG CAT GG -3' (Fragment 619) (SEQ. ID NO:626)
5'-
      GAT GGA GGG CGG CAT G -3' (Fragment 620) (SEO. ID NO:627)
      GAT GGA GGG CGG CAT -3' (Fragment 621) (SEQ. ID NO:628)
5'-
      GAT GGA GGG CGG CA-3' (Fragment 622) (SEQ. ID NO:629)
      GAT GGA GGG CGG C-3' (Fragment 623) (SEQ. ID NO:630)
      GAT GGA GGG CGG -3' (Fragment 624) (SEQ. ID NO:631)
5'-
      GAT GGA GGG CG -3' (Fragment 625) (SEQ. ID NO:632)
      GAT GGA GGG C -3' (Fragment 626) (SEQ. ID NO:633)
      AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 627) (SEQ. ID NO:634)
      AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 628) (SEQ. ID NO:635)
5'-
      AT GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 629) (SEQ. ID NO:636)
      AT GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 630) (SEQ. ID NO:637)
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```
AT GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 631) (SEQ. 1D NO:638)
     AT GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 632) (SEQ. ID NO:639)
     AT GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 633) (SEQ. ID NO:640) AT GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 634) (SEQ. ID NO:641)
5'-
5'-
     AT GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 635) (SEQ. ID NO:642)
     AT GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 636) (SEQ. ID NO:643)
     AT GGA GGG CGG CAT GGC GGG CA-3' (Fragment 637) (SEQ. ID NO:644)
5'-
     AT GGA GGG CGG CAT GGC GGG C-3' (Fragment 638) (SEQ. ID NO:645)
     AT GGA GGG CGG CAT GGC GGG -3' (Fragment 639) (SEQ. ID NO:646)
     AT GGA GGG CGG CAT GGC GG-3' (Fragment 640) (SEQ. ID NO:647)
5'-
     AT GGA GGG CGG CAT GGC G-3' (Fragment 641) (SEQ. ID NO:648)
     AT GGA GGG CGG CAT GGC -3' (Fragment 642) (SEQ. ID NO:649)
5'-
     AT GGA GGG CGG CAT GG -3' (Fragment 643) (SEQ. ID NO:650)
5'-
     AT GGA GGG CGG CAT G -3' (Fragment 644) (SEQ. ID NO:651)
5'-
     AT GGA GGG CGG CAT -3' (Fragment 645) (SEQ. ID NO:652)
     AT GGA GGG CGG CA-3' (Fragment 646) (SEQ. ID NO:653)
5'-
     AT GGA GGG CGG C-3' (Fragment 647) (SEQ. ID NO:654)
5'-
     AT GGA GGG CGG -3' (Fragment 648) (SEQ. ID NO:655)
     AT GGA GGG CG -3' (Fragment 649) (SEQ. ID NO:656)
5'-
     T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 650) (SEQ. ID NO:657)
     T GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 651) (SEQ. ID NO:658) T GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 652) (SEQ. ID NO:659)
5'-
5'-
     T GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 653) (SEQ. ID NO:660)
5'-
     T GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 654) (SEQ. ID NO:661) T GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 655) (SEQ. ID NO:662)
5'-
     T GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 656) (SEQ. ID NO:663)
5'-
     T GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 657) (SEQ. ID NO:664)
     T GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 658) (SEQ. ID NO:665)
5'-
     T GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 659) (SEQ. ID NO:666)
5'-
     T GGA GGG CGG CAT GGC GGG CA-3' (Fragment 660) (SEQ. ID NO:667)
     T GGA GGG CGG CAT GGC GGG C-3' (Fragment 661) (SEQ. ID NO:668)
     T GGA GGG CGG CAT GGC GGG -3' (Fragment 662) (SEQ. ID NO:669)
5'-
     T GGA GGG CGG CAT GGC GG-3' (Fragment 663) (SEQ. ID NO:670)
     T GGA GGG CGG CAT GGC G-3' (Fragment 664) (SEQ. ID NO:671)
5'-
     T GGA GGG CGG CAT GGC -3' (Fragment 665) (SEQ. ID NO:672)
5'-
     T GGA GGG CGG CAT GG -3' (Fragment 666) (SEQ. ID NO:673)
     T GGA GGG CGG CAT G -3' (Fragment 667) (SEQ. ID NO:674)
5'-
     T GGA GGG CGG CAT -3' (Fragment 668) (SEQ. ID NO:675)
5'-
     T GGA GGG CGG CA-3' (Fragment 669) (SEQ. ID NO:676)
     T GGA GGG CGG C-3' (Fragment 670) (SEQ. ID NO:677)
5'-
     T GGA GGG CGG -3' (Fragment 671) (SEQ. ID NO:678)
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 672) (SEQ. ID NO:679)
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 673) (SEQ. ID NO:680)
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 674) (SEQ. ID NO:681)
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 675) (SEQ. ID NO:682)
     GGA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 676) (SEQ. ID NO:683)
5'-
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 677) (SEQ. ID NO:684)
5'-
     GGA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 678) (SEQ. ID NO:685)
     GGA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 679) (SEQ. ID NO:686)
5'-
     GGA GGG CGG CAT GGC GGG CAC A-3' (Fragment 680) (SEQ. ID NO:687)
5'-
     GGA GGG CGG CAT GGC GGG CAC-3' (Fragment 681) (SEQ. ID NO:688)
     GGA GGG CGG CAT GGC GGG CA-3' (Fragment 682) (SEQ. ID NO:689)
5'-
     GGA GGG CGG CAT GGC GGG C-3' (Fragment 683) (SEQ. ID NO:690)
5'-
     GGA GGG CGG CAT GGC GGG -3' (Fragment 684) (SEQ. ID NO:691)
     GGA GGG CGG CAT GGC GG-3' (Fragment 685) (SEQ. ID NO:692)
5'-
     GGA GGG CGG CAT GGC G-3' (Fragment 686) (SEQ. ID NO:693)
5'-
     GGA GGG CGG CAT GGC -3' (Fragment 687) (SEQ. ID NO:694)
5'-
     GGA GGG CGG CAT GG -3' (Fragment 688) (SEQ. ID NO:695)
5'-
     GGA GGG CGG CAT G -3' (Fragment 689) (SEQ. ID NO:696)
5'-
     GGA GGG CGG CAT -3' (Fragment 690) (SEQ. ID NO:697)
5'-
     GGA GGG CGG CA-3' (Fragment 691) (SEQ. ID NO:698)
5'-
     GGA GGG CGG C-3' (Fragment 692) (SEQ. ID NO:699)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 693) (SEQ. ID NO:700)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 694) (SEQ. ID NO:701)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 695) (SEQ. ID NO:702)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 696) (SEQ. ID NO:703)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 697) (SEQ. ID NO:704)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 698) (SEQ. ID NO:705)
5'-
     GA GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 699) (SEQ. ID NO:706)
5'-
     GA GGG CGG CAT GGC GGG CAC AG-3' (Fragment 700) (SEQ. ID NO:707)
5'-
     GA GGG CGG CAT GGC GGG CAC A-3' (Fragment 701) (SEQ. ID NO:708)
5'-
     GA GGG CGG CAT GGC GGG CAC-3' (Fragment 702) (SEQ. ID NO:709)
     GA GGG CGG CAT GGC GGG CA-3' (Fragment 703) (SEQ. ID NO:710)
5'-
     GA GGG CGG CAT GGC GGG C-3' (Fragment 704) (SEQ. ID NO:711)
     GA GGG CGG CAT GGC GGG -3' (Fragment 705) (SEQ. ID NO:712)
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GA GGG CGG CAT GGC GG-3' (Fragment 706) (SEQ. ID NO:713) GA GGG CGG CAT GGC G-3' (Fragment 707) (SEQ. ID NO:714) GA GGG CGG CAT GGC -3' (Fragment 708) (SEQ. ID NO:715) 5'-GA GGG CGG CAT GG -3' (Fragment 709) (SEQ. ID NO:716) GA GGG CGG CAT G -3' (Fragment 710) (SEQ. ID NO:717) GA GGG CGG CAT -3' (Fragment 711) (SEQ. ID NO:718) GA GGG CGG CA-3' (Fragment 712) (SEQ. ID NO:719) A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 713) (SEQ. ID NO:720) A GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 714) (SEQ. ID NO:721) A GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 715) (SEQ. ID NO:722) A GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 716) (SEQ. ID NO:723) A GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 717) (SEQ. ID NO:724) A GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 718) (SEQ. ID NO:725) A GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 719) (SEQ. ID NO:726) A GGG CGG CAT GGC GGG CAC AG-3' (Fragment 720) (SEQ. ID NO:727) A GGG CGG CAT GGC GGG CAC A-3' (Fragment 721) (SEQ. ID NO:728) A GGG CGG CAT GGC GGG CAC-3' (Fragment 722) (SEQ. ID NO:729) A GGG CGG CAT GGC GGG CA-3' (Fragment 723) (SEQ. ID NO:730) A GGG CGG CAT GGC GGG C-3' (Fragment 724) (SEQ. ID NO:731) A GGG CGG CAT GGC GGG -3' (Fragment 725) (SEQ. ID NO:732) A GGG CGG CAT GGC GG-3' (Fragment 726) (SEQ. ID NO:733) A GGG CGG CAT GGC G-3' (Fragment 727) (SEQ. ID NO:734) A GGG CGG CAT GGC -3' (Fragment 728) (SEQ. ID NO:735) A GGG CGG CAT GG -3' (Fragment 729) (SEQ. ID NO:736) A GGG CGG CAT G -3' (Fragment 730) (SEQ. ID NO:737) A GGG CGG CAT -3' (Fragment 731) (SEQ. ID NO:738) GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 732) (SEQ. ID NO:739) GGG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 733) (SEQ. ID NO:740) 5'-GGG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 734) (SEQ. ID NO:741) GGG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 735) (SEQ. ID NO:742) GGG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 736) (SEQ. ID NO:743) GGG CGG CAT GGC GGG CAC AGG C-3' (Fragment 737) (SEQ. ID NO:744) GGG CGG CAT GGC GGG CAC AGG -3' (Fragment 738) (SEQ. ID NO:745) GGG CGG CAT GGC GGG CAC AG-3' (Fragment 739) (SEQ. ID NO:746) GGG CGG CAT GGC GGG CAC A-3' (Fragment 740) (SEQ. ID NO:747) 5'-GGG CGG CAT GGC GGG CAC-3' (Fragment 741) (SEQ. ID NO:748) GGG CGG CAT GGC GGG CA-3' (Fragment 742) (SEQ. ID NO:749) 5'-GGG CGG CAT GGC GGG C-3' (Fragment 743) (SEQ. ID NO:750) GGG CGG CAT GGC GGG -3' (Fragment 744) (SEQ. ID NO:751) GGG CGG CAT GGC GG-3' (Fragment 745) (SEQ. ID NO:752) 5'-GGG CGG CAT GGC G-3' (Fragment 746) (SEQ. ID NO:753) GGG CGG CAT GGC -3' (Fragment 747) (SEQ. ID NO:754) 5'-GGG CGG CAT GG -3' (Fragment 748) (SEQ. ID NO:755) GGG CGG CAT G -3' (Fragment 749) (SEQ. ID NO:756) GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 750) (SEQ. ID NO:757) GG CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 751) (SEQ. ID NO:758) 5'-GG CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 752) (SEQ. ID NO:759) 5'-GG CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 753) (SEQ. ID NO:760) 5'-GG CGG CAT GGC GGG CAC AGG CT-3' (Fragment 754) (SEQ. ID NO:761) GG CGG CAT GGC GGG CAC AGG C-3' (Fragment 755) (SEQ. ID NO:762) GG CGG CAT GGC GGG CAC AGG -3' (Fragment 756) (SEQ. ID NO:763) 5'-GG CGG CAT GGC GGG CAC AG-3' (Fragment 757) (SEQ. ID NO:764) 5'-GG CGG CAT GGC GGG CAC A-3' (Fragment 758) (SEQ. ID NO:765) GG CGG CAT GGC GGG CAC-3' (Fragment 759) (SEQ. ID NO:766) 5'-GG CGG CAT GGC GGG CA-3' (Fragment 760) (SEQ. ID NO:767) GG CGG CAT GGC GGG C-3' (Fragment 761) (SEQ. ID NO:768) GG CGG CAT GGC GGG -3' (Fragment 762) (SEQ. ID NO:769) GG CGG CAT GGC GG-3' (Fragment 763) (SEQ. ID NO:770) GG CGG CAT GGC G-3' (Fragment 764) (SEQ. ID NO:771) GG CGG CAT GGC -3' (Fragment 765) (SEQ. ID NO:772) GG CGG CAT GG -3' (Fragment 766) (SEQ. ID NO:773) G CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 767) (SEO. ID NO:774) G CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 768) (SEQ. ID NO:775) G CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 769) (SEQ. ID NO:776) G CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 770) (SEQ. ID NO:777) G CGG CAT GGC GGG CAC AGG CT-3' (Fragment 771) (SEQ. ID NO:778) G CGG CAT GGC GGG CAC AGG C-3' (Fragment 772) (SEQ. ID NO:779) G CGG CAT GGC GGG CAC AGG -3' (Fragment 773) (SEQ. ID NO:780) G CGG CAT GGC GGG CAC AG-3' (Fragment 774) (SEQ. ID NO:781) G CGG CAT GGC GGG CAC A-3' (Fragment 775) (SEQ. ID NO:782) G CGG CAT GGC GGG CAC-3' (Fragment 776) (SEQ. ID NO:783) G CGG CAT GGC GGG CA-3' (Fragment 777) (SEQ. ID NO:784) G CGG CAT GGC GGG C-3' (Fragment 778) (SEQ. ID NO:785) G CGG CAT GGC GGG -3' (Fragment 779) (SEQ. ID NO:786) G CGG CAT GGC GG-3' (Fragment 780) (SEQ. ID NO:787)

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G CGG CAT GGC G-3' (Fragment 781) (SEQ. ID NO:788)
G CGG CAT GGC -3' (Fragment 782) (SEQ. ID NO:789)
CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 783) (SEQ. ID NO:790)
CGG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 784) (SEQ. ID NO:791)
CGG CAT GGC GGG CAC AGG CTG G-3' (Fragment 785) (SEQ. ID NO:792)
CGG CAT GGC GGG CAC AGG CTG -3' (Fragment 786) (SEQ. ID NO:793)
CGG CAT GGC GGG CAC AGG CT-3' (Fragment 787) (SEQ. ID NO:794)
CGG CAT GGC GGG CAC AGG C-3' (Fragment 788) (SEQ. ID NO:795)
CGG CAT GGC GGG CAC AGG -3' (Fragment 789) (SEQ. ID NO:796)
CGG CAT GGC GGG CAC AG-3' (Fragment 790) (SEQ. ID NO:797)
CGG CAT GGC GGG CAC A-3' (Fragment 791) (SEQ. ID NO:798)
CGG CAT GGC GGG CAC-3' (Fragment 792) (SEQ. ID NO:799)
CGG CAT GGC GGG CA-3' (Fragment 793) (SEQ. ID NO:800)
CGG CAT GGC GGG C-3' (Fragment 794) (SEQ. ID NO:801)
CGG CAT GGC GGG -3' (Fragment 795) (SEQ. ID NO:802)
CGG CAT GGC GG-3' (Fragment 796) (SEQ. ID NO:803)
CGG CAT GGC G-3' (Fragment 797) (SEQ. ID NO:804)
GG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 798) (SEQ. ID NO:805)
GG CAT GGC GGG CAC AGG CTG GG-3' (Fragment 799) (SEQ. ID NO:806)
GG CAT GGC GGG CAC AGG CTG G-3' (Fragment 800) (SEQ. ID NO:807)
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GG CAT GGC GGG CAC AGG CT-3' (Fragment 802) (SEQ. ID NO:809)
GG CAT GGC GGG CAC AGG C-3' (Fragment 803) (SEQ. ID NO:810)
GG CAT GGC GGG CAC AGG -3' (Fragment 804) (SEQ. ID NO:811)
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GG CAT GGC GG-3' (Fragment 811) (SEQ. ID NO:818)
G CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 812) (SEQ. ID NO:819)
G CAT GGC GGG CAC AGG CTG GG-3' (Fragment 813) (SEQ. ID NO:820)
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G CAT GGC GGG CAC AGG C-3' (Fragment 817) (SEQ. ID NO:824)
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 G CAT GGC GGG -3' (Fragment 824) (SEQ. ID NO:831)
 CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 825) (SEQ. ID NO:832)
 CAT GGC GGG CAC AGG CTG GG-3' (Fragment 826) (SEQ. 1D NO:833)
 CAT GGC GGG CAC AGG CTG G-3' (Fragment 827) (SEQ. ID NO:834)
 CAT GGC GGG CAC AGG CTG -3' (Fragment 828) (SEQ. ID NO:835)
 CAT GGC GGG CAC AGG CT-3' (Fragment 829) (SEQ. ID NO:836)
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 CAT GGC GGG CAC-3' (Fragment 834) (SEQ. ID NO:841)
 CAT GGC GGG CA-3' (Fragment 835) (SEQ. ID NO:842)
 CAT GGC GGG C-3' (Fragment 836) (SEQ. ID NO:843)
 AT GGC GGG CAC AGG CTG GGC-3' (Fragment 837) (SEQ. ID NO:844)
 AT GGC GGG CAC AGG CTG GG-3' (Fragment 838) (SEQ. ID NO:845)
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 AT GGC GGG CAC AGG CT-3' (Fragment 841) (SEQ. ID NO:848)
 AT GGC GGG CAC AGG C-3' (Fragment 842) (SEQ. ID NO:849)
  AT GGC GGG CAC AGG -3' (Fragment 843) (SEQ. ID NO:850)
 AT GGC GGG CAC AG-3' (Fragment 844) (SEQ. ID NO:851)
 AT GGC GGG CAC A-3' (Fragment 845) (SEQ. ID NO:852)
  AT GGC GGG CAC-3' (Fragment 846) (SEQ. ID NO:853)
  AT GGC GGG CA-3' (Fragment 847) (SEQ. ID NO:854)
 T GGC GGG CAC AGG CTG GGC-3' (Fragment 848) (SEQ. ID NO:855)
 T GGC GGG CAC AGG CTG GG-3' (Fragment 849) (SEQ. ID NO:856)
  T GGC GGG CAC AGG CTG G-3' (Fragment 850) (SEQ. ID NO:857)
 T GGC GGG CAC AGG CTG -3' (Fragment 851) (SEQ. ID NO:858)
  T GGC GGG CAC AGG CT-3' (Fragment 852) (SEQ. ID NO:859)
  T GGC GGG CAC AGG C-3' (Fragment 853) (SEQ. ID NO:860)
  T GGC GGG CAC AGG -3' (Fragment 854) (SEQ. ID NO:861)
  T GGC GGG CAC AG-3' (Fragment 855) (SEQ. ID NO:862)
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T GGC GGG CAC A-3' (Fragment 856) (SEQ. ID NO:863) 5'-T GGC GGG CAC-3' (Fragment 857) (SEQ. ID NO:864) 5'-GGC GGG CAC AGG CTG GGC-3' (Fragment 858) (SEQ. ID NO:865) 5'-GGC GGG CAC AGG CTG GG-3' (Fragment 859) (SEQ. ID NO:866) 5'-GGC GGG CAC AGG CTG G-3' (Fragment 860) (SEQ. ID NO:867) 5'-GGC GGG CAC AGG CTG -3' (Fragment 861) (SEQ. ID NO:868) 5'-GGC GGG CAC AGG CT-3' (Fragment 862) (SEQ. ID NO:869) 5'-GGC GGG CAC AGG C-3' (Fragment 863) (SEQ. ID NO:870) 5'-GGC GGG CAC AGG -3' (Fragment 864) (SEQ. ID NO:871) 5'-GGC GGG CAC AG-3' (Fragment 865) (SEQ. ID NO:872) 5'-GGC GGG CAC A-3' (Fragment 866) (SEQ. ID NO:873) 5'-GC GGG CAC AGG CTG GGC-3' (Fragment 867) (SEQ. ID NO:874) 5'-GC GGG CAC AGG CTG GG-3' (Fragment 868) (SEQ. ID NO:875) 5'-GC GGG CAC AGG CTG G-3' (Fragment 869) (SEQ. ID NO:876) 5'-GC GGG CAC AGG CTG -3' (Fragment 870) (SEQ. ID NO:877) GC GGG CAC AGG CT-3' (Fragment 871) (SEQ. ID NO:878) 5'-5'-GC GGG CAC AGG C-3' (Fragment 872) (SEQ. ID NO:879) 5'-GC GGG CAC AGG -3' (Fragment 873) (SEQ. ID NO:880) 5'-GC GGG CAC AG-3' (Fragment 874) (SEQ. ID NO:881) 5'-C GGG CAC AGG CTG GGC-3' (Fragment 875) (SEQ. ID NO:882) 5'-C GGG CAC AGG CTG GG-3' (Fragment 876) (SEQ. ID NO:883) 5'-C GGG CAC AGG CTG G-3' (Fragment 877) (SEQ. ID NO:884) 5'-C GGG CAC AGG CTG -3' (Fragment 878) (SEQ. ID NO:885) 5'-C GGG CAC AGG CT-3' (Fragment 879) (SEQ. ID NO:886) 5'-C GGG CAC AGG C-3' (Fragment 880) (SEQ. ID NO:887) 5'-C GGG CAC AGG -3' (Fragment 881) (SEQ. ID NO:888) 5'-GGG CAC AGG CTG GGC-3' (Fragment 882) (SEQ. ID NO:889) 5'-GGG CAC AGG CTG GG-3' (Fragment 883) (SEQ. ID NO:890) 5'-GGG CAC AGG CTG G-3' (Fragment 884) (SEQ. ID NO:891) 5'-GGG CAC AGG CTG -3' (Fragment 885) (SEQ. ID NO:892) 5'-GGG CAC AGG CT-3' (Fragment 886) (SEQ. ID NO:893) 5'-GGG CAC AGG C-3' (Fragment 887) (SEQ. ID NO:894) 5'-GG CAC AGG CTG GGC-3' (Fragment 888) (SEQ. ID NO:895) 5'-GG CAC AGG CTG GG-3' (Fragment 889) (SEQ. ID NO:896) 5'-GG CAC AGG CTG G-3' (Fragment 890) (SEQ. ID NO:897) 5'-GG CAC AGG CTG -3' (Fragment 891) (SEQ. ID NO:898) 5'-GG CAC AGG CT-3' (Fragment 892) (SEQ. ID NO:899) 5'-G CAC AGG CTG GGC-3' (Fragment 893) (SEQ. ID NO:900) 5'-G CAC AGG CTG GG-3' (Fragment 894) (SEQ. ID NO:901) 5'-G CAC AGG CTG G-3' (Fragment 895) (SEQ. ID NO:902) . 5'-G CAC AGG CTG -3' (Fragment 896) (SEQ. ID NO:903) -5'-CAC AGG CTG GGC-3' (Fragment 897) (SEQ. ID NO:904) CAC AGG CTG GG-3' (Fragment 898) (SEQ. ID NO:905) 5'-5'-CAC AGG CTG G-3' (Fragment 899) (SEQ. ID NO:906) 5'-AC AGG CTG GGC-3' (Fragment 900) (SEQ. ID NO:907) 5'-AC AGG CTG GG-3' (Fragment 901) (SEQ. ID NO:908) C AGG CTG GGC-3' (Fragment 902) (SEQ. ID NO:909) 5'-GGC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 903) (SEQ. ID NO:910) 5'-GC GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 904) (SEQ. ID NO:911) S'-C GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 905) (SEQ. ID NO:912) 5'-GGC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 906) (SEQ. ID NO:913) 5'-GC CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 907) (SEQ. ID NO:914) 5'-C CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 908) (SEQ. ID NO:915) 5'-CTG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 909) (SEQ. ID NO:916) 5'-TG GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(Fragment 910) (SEQ. ID NO:917) 5'-G GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 911) (SEQ. ID NO:918) 5'-GAA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 912) (SEQ. ID NO:919) 5'-AA AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 913) (SEQ. ID NO:920) 5'-A AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 914) (SEQ. ID NO:921) 5'-AGC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3'(Fragment 915) (SEQ. ID NO:922) 5'-GC TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 916) (SEQ. ID NO:923) 5'-C TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 917) (SEQ. ID NO:924) 5'-TGA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 918) (SEQ. ID NO:925) 5'-GA GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 919) (SEQ. ID NO:926) 5'-A GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 920) (SEQ. ID NO:927) 5'-GAT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 921) (SEQ. ID NO:928) 5'-AT GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 922) (SEQ. ID NO:929) 5'-T GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 923) (SEQ. ID NO:930) 5'-GGA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 924) (SEQ. ID NO:931) 5'-GA GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 925) (SEQ. ID NO:932)

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5'-A GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 926) (SEQ. ID NO:933)
5'-GGG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 927) (SEQ. ID NO:934)
5'-GG CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 928) (SEQ. ID NO:935)
5'-G CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 929) (SEQ. ID NO:936)
5'-CGG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 930) (SEQ. ID NO:937)
5'-GG CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 931) (SEQ. ID NO:938)
5'-G CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 932) (SEQ. ID NO:939)
5'-CAT GGC GGG CAC AGG CTG GGC-3' (Fragment 933) (SEQ. ID NO:940)
5'-AT GGC GGG CAC AGG CTG GGC-3' (Fragment 934) (SEQ. ID NO:941)
5'-T GGC GGG CAC AGG CTG GGC-3' (Fragment 935) (SEQ. ID NO:942)
5'-GGC GGG CAC AGG CTG GGC-3' (Fragment 936) (SEQ. ID NO:943)
5'-GC GGG CAC AGG CTG GGC-3' (Fragment 937) (SEQ. ID NO:944)
5'-C GGG CAC AGG CTG GGC-3' (Fragment 938) (SEQ. ID NO:945)
5'-GGG CAC AGG CTG GGC-3' (Fragment 939) (SEQ. ID NO:946)
5'-GG CAC AGG CTG GGC-3' (Fragment 940) (SEQ. ID NO:947)
5'-G CAC AGG CTG GGC-3' (Fragment 941) (SEQ. ID NO:948)
5'-CAC AGG CTG GGC-3' (Fragment 942) (SEQ. ID NO:949)
5'-AC AGG CTG GGC-3' (Fragment 943) (SEQ. ID NO:950)
5'-C AGG CTG GGC-3' (Fragment 944) (SEQ. ID NO:951)
5'-AGG CTG GGC-3' (Fragment 945) (SEQ. ID NO: 952)
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Other adenosine fragments, for example those with low adenosine content or lacking adenosine altogether, are also suitable and in some cases even preferred, for use with the invention. The following sequences, their fragments and combinations, are one particularly preferred group of anti-sense oligos.

```
TTT TCC TTC CTT TGT CTC TCT TC (FRAG 946) (SEQ. ID NO: 953)
GCT CCC GGC TGC CTG (FRAG 947) (SEQ. ID NO: 954)
CTC GGC CGT GCG GCT CTG TCG CTC CCG GT (FRAG 948) (SEQ. ID NO: 955)
CCG CCG CCC TCC GGG GGG TC (FRAG 949) (SEQ. ID NO: 956)
TGC TGC CGT TGG CTG CCC (FRAG 950) (SEQ. ID NO: 957)
CTT CTG CGG GTC GCC GG (FRAG 951) (SEQ. ID NO: 958)
TGC TGG GCT TGT GGC (FRAG 952) (SEQ. ID NO: 959)
GGC CTC TCT TCT GGG (FRAG 953) (SEQ. ID NO: 960)
CCT GGT CCC TCC GT (FRAG 954) (SEQ. ID NO: 961)
GGT GGC TCC TCT GC (FRAG 955) (SEQ. ID NO: 962)
GCT TGG TCC TGG GGC TGC (FRAG 956) (SEQ. ID NO: 963)
TGC TCT CCT CTC CTT (FRAG 957) (SEQ. ID NO: 964)
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In another embodiment of this invention, the oligos are anti-sense to an adenosine  $A_{2a}$  receptor, and must either "up-regulate" it, or if they have some adenosine  $A_1$  activity they are treated as the other anti-sense oligos. The following sequences are preferred examples of anti-sense oligos associated with the human adenosine  $A_{2a}$  receptor. Another preferred group is composed of fragments of these sequences as generally described above, and combinations thereof, as well as mixtures. Also preferred are these sequences, fragments and their combinations where one or more adenosines are substituted by a universal base or an adenosine analogue which either is not an agonist or a ligand for the adenosine  $A_1$  receptor, or which acts as an antagonist of the  $A_1$  receptor, such as, for example, the ophylline or enprophylline.

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5'-TGC TTT TCT TTT CTG GGC CTC-3' (FRAG 958) (SEQ. ID NO: 965)
5'-TGT GGT CTG TTT TTT TCT G-3' (FRAG 959) (SEQ. ID NO: 966)
5'-GCC CTG CTG GGG CGC TCT CC-3' (FRAG 960) (SEQ. ID NO: 967)
5'-GCC GCC CTG GCT CCC-3' (FRAG 961) (SEQ. ID NO: 968)
5'-GGB GCC CBT GBT GGG CBT GCC-3' (FRAG 962) (SEQ. ID NO: 969)
5'-CTG GTT CTT GCC CTC CTT TGG CTG-3' (FRAG 963) (SEQ. ID NO: 970)
5'-CCG TGC CCG CTC CCC GGC-3' (FRAG 964) (SEQ. ID NO: 971)
5'-CTC CTG GCG GGT GGC CGT TG-3' (FRAG 965) (SEQ. ID NO: 972)
5'-GGC CCG TGT TCC CCT GGG-3' (FRAG 966) (SEQ. ID NO: 973)
5'-GCC TGG GGC TCC CTT CTC TC-3' (FRAG 967) (SEQ. ID NO: 974)
5'-TGC TGC TGC TGG TGC TGC TGC CCC -3' (FRAG 969) (SEQ. ID NO: 975)
5'-TGC TGC TGC TGG TGC TGT GGC CCC C-3' (FRAG 969) (SEQ. ID NO: 976)
GTACACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC (FRAG 970) (SEQ. ID NO: 977)
GTBCBCCGBGGGGCCCCBTGBTGGGCCBTGCCBCBGBCGBCGGC (FRAG 971) (SEQ. ID NO: 978)
```

As indicated above, also included in this patent are all types of adenosine  $A_{2a}$  agonists, whether or not they are nucleic acids. These are known in the art and must generally have agonistic  $A_{2a}$  activity and either lack or have low adenosine  $A_1$  agonistic activity and/or have antagonistic adenosine  $A_1$  activity.

In another embodiment, the anti-sense oligo of the invention may be a sequence which is antisense to the adenosine  $A_{2b}$  receptor. By means of example, the following sequences associated with the human receptor are provided. These sequences as well as their fragments and combinations, desadenosine fragments and those where one or more A are substituted with a universal base or adenosine analogue as described above are preferred.

```
5'-GGC GCC GTG CCG CGT CTT GGT GGC GGC GG-3' (FRAG 972) (SEQ. ID NO: 979)
5'-GTT CGC GCC CGC GCG GGG CCC CTC CGG TCC-3' (FRAG 973) (SEQ. ID NO: 980)
5'-TTG GCC CGC GCG CCC GCC CGT CTC GGG CTG GGC GG-3 (FRAG 974) (SEQ. ID NO: 981)
5'-CGG GTC GGG GCC CCC CGC GGC C-3' (FRAG 975) (SEQ. ID NO: 982)
5'-GCC TCG GGG CTG GGG CGC TGG TGG CCG GG-3' (FRAG 976) (SEQ. ID NO: 983)
5'-CCG CGC CTC CGC CTG CCG CTT CTG-3' (FRAG 977) (SEQ. ID NO: 984)
5'-GCT GGG CCC CGG GCG CCC CCT-3' (FRAG 978) (SEQ. ID NO: 985)
5'-CCC CTC TTG CTC GGG TCC CCG TG-3' (FRAG 979) (SEQ. ID NO: 986)
ACAGCGCGTCCTGTGTCTCCAGCAGCATGGCCGGGCCAGCTGGGCCCC (FRAG 980) (SEQ. ID NO: 987)
BCBGCGCGTCCTGTGTCTCCBGCBGCBTGGCCCGGGCCBGCTGGGCCCC (FRAG 981) (SEQ. ID NO: 988)
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In still another embodiment, the oligo of this invention may be anti-sense to any fragment of the adenosine A₃ receptor gene or mRNA, including overlapping regions with the flanking regions or introns. The following are examples of these fragments associated with the human receptor. These are preferred sequences. Also preferred are their fragments and combinations, as well as desadenosine fragments and those where one or more A are substituted by a universal base or A analogue as described above.

```
ACA GAG CA TGC TGT TGT TGG GCA TCT TGC CTT CCC AGG G (FRAG 982) (SEQ. ID NO: 989) BCB GBG CB TGC TGT TGT TGG GCB TCT TGC CTT CCC BGG G (FRAG 983) (SEQ. ID NO: 990) CCC TTT TCT GGT GGG GTG (FRAG 984) (SEQ. ID NO: 994) GTG CTG TTG TTG GGC (FRAG 985) (SEQ. ID NO: 992) TTT CTT CTT CTC (FRAG 986) (SEQ. ID NO: 993) CCC TTT TCT GGT GGG GTG (FRAG 987) (SEQ. ID NO: 994) GTG CTG TTG TTG GGC (FRAG 988) (SEQ. ID NO: 995) TTT CTT CTG TTC CC (FRAG 989) (SEQ. ID NO: 996)
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In the anti-sense oligonucleotides of the present invention, exemplified by the preceding sequences, a number of adenosine bases may be replaced with an appropriate "spacer" or universal base (e.g.,  $1-[\beta-D-2]$ -deoxyribofuranosyl]-5-nitroindole], or with an adenosine agonist or antagonist that does not stimulate (or inhibit) adenosine  $A_1$ ,  $A_{2b}$  or  $A_3$  receptors but may stimulate the  $A_{2a}$  receptor. A preferred universal base for the treatment of SVT is one that exhibits adenosine  $A_{2a}$  agonsitic activity. In this manner, a specific adenosine receptor gene may be targeted to obtain one or more anti-sense oligonucleotide(s) (oligos) that selectively bind(s) to the corresponding mRNA, and then, if necessary, their content of adenosine may be reduced by substituting one or more universal bases or adenosine analogues incapable of activating adenosine  $A_1$ ,  $A_{2b}$  or  $A_3$  receptors or which activate the adenosine  $A_{2a}$  receptor. Thus, in addition to "down-regulating" specific adenosine receptor genes, the present oligos have an increased effect when administered by either selection of genes, RNA and flanking regions that are devoid, or have a low A content, or alternatively one or more of the adenosine(s) present in the

oligonucleotide(s) are substituted with other nucleotide bases, so called universal bases, which bind to thymidine (T) but lack the ability to activate adenosine receptors and otherwise may not activate adenosine receptors. Given that adenosine (A) is a nucleotide base complementary to thymidine (T), when a T appears in the RNA, the anti-sense oligo will have an A at the same position.

The method of the present invention may be used to treat ailments associated with or causing cardiac, lung and/or renal damage, and even failure in a subject, regardless of its cause. The anti-sense agent(s) of the invention have preferably a low (or reduced) A content to prevent its liberation upon in vivo degradation of the agent(s), preferably up to about 15%, more preferably up to about 10%, still more preferably up to about 5%, and even more preferred being devoid of A ("desadenosine oligos").

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotides long which comprises the selected fragment and has a C and G nucleic acid content of up to and including about 15%. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotides long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%. This method may also comprise, when the selected fragment comprises at least one thymidine base, substituting an adenosine base in the corresponding nucleotide of the anti-sense fragment with a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A₁, A_{2b} and A₃ receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A2a receptor. The analogue heteroaromatic bases may be selected from all pyrimidines and purines, which may be substituted by O, halo, NH₂, SH, SO, SO₂, SO₃, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkylaryl, alkenylaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH₂, primary, secondary and tertiary amine, SH, SO, SO₂, SO₃, cycloalkyl, heterocycloalkyl and heteroaryl. The pyrimidines and purines may be substituted at all positions as is known in the art, but preferred are those which are substituted at positions 1, 2, 3, 4, 7 and/or 8. More preferred are pyrimidines and purines such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein R¹ and R² are independently H, alkyl, alkenyl or alkynyl and R³ is H, aryl, dicycloalkyl, dicycloalkenyl, dicycloalkynyl, cycloalkynyl, cycloalkynyl, cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, O-cycloalkynyl, NH₂-alkylamino-ketoxyalkyloxy-aryl, mono and dialkylaminoalkyl-N-alkylamino-SO₂aryl, among others. However, other methods may also be employed. The inventor reduced the

adenosine content of the anti-sense oligos corresponding to the thymidines (T) present in the target gene, RNA, flanking regions, and bridging sections to less than about 15%, or fully eliminated A from the oligonucleotide sequence as a means for preventing their breakdown products from freeing adenosine into the lung tissue environment and, thereby, aggravating the subject's ailment and/or countering the beneficial effect of the administered agent.

Also part of this invention are chemical analogues of oligonucleotides in which, for example, the phosphodiester bonds have been modified, e.g., to a methylphosphonate, a phosphotriester, a phosphorothioate, a phosphorodithioate, or a phosphoramidate, or that other portions of the molecule have been modified, so as to render the oligonucleotide more stable in vivo. The naturally occurring phosphodiester linkages in oligonucleotides are susceptible to degradation by endogenously occurring cellular nucleases, while many analogous linkages are highly resistant to nuclease degradation. See Milligan et al., and Cohen, J. S., supra. The use of a "3'-end cap" strategy by which nuclease-resistant linkages are substituted for phosphodiester linkages at the 3'-end of the oligonucleotide protects oligonucleotides from degradation. See, Tidd, D. M. and Warenius, H.M., Br. J. Cancer 60, 343-350 (1989); Shaw, J.P. et al., Nucleic Acids Res. 19, 747-750 (1991). Phosphoramidate, phosphorothioate, and methylphosphonate linkages are suitable for use in this invention. In addition, extensive modification of the phosphodiester backbone has been shown to impart stability and may allow for enhanced affinity and increased cellular permeation of oligonucleotides. See Milligan, et al., supra. Many different chemical strategies have been employed to replace the entire phosphodiester backbone with novel linkages. Id. The analogues of the oligonucleotides of the invention include phosphorothicate, phosphorodithioate. methylphosphonate, phosphoramidate, boranophosphate, formacetal, 2'-0-methyl, 3'-thioformacetal, 5'-thioformacetal, 5'-thioether, carbonate, 5'-N-carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene (methylimino) (MMI) and methyleneoxy (methylimino) (MOMI) linkages, among others. The oligonucleotides of the invention may also be modified by addition of a terminal 1,3-propanediol or a terminal dodecanol, among others, or they may be conjugated to a polyethylene glycol, cholesterol, cholesteryl, dehydroepiandrosterone, dehydroepiandrosterone sulfate, dehydroepiandrosterone sulfatide, ubiquinone, dolichol, poly L-lysine, sulfatidic acid and fatty acid, among others. The oligos of the invention may also be modified by 2'-O-methoxyethy, C-5-propynyl pyrimidine, C-5 methyl cytidine, C-5 ethynyl pyrimidine, 2'-propoxy, C-18 amine, N3'-P5' phosphoramidates, 3'-alkylamino, 2'-fluoro; 5-fluoro pyrimidine, 5-iodo pyrimidine, 5-bromo pyrimidine, 2'-borano, C-5 hexynyl pyrimidine, 2'-O-(2-methoxy)ethyl, 2'-O-aminopropyl, 5-(phenylethyl) and peptide nucleic acid interbase linkages. Phosphorothioate and methylphosphonate-modified oligonucleotides are particularly preferred because of their availability and suitability for automated oligonucleotide synthesis. oligonucleotides containing modifications to the nucleotide base itself (e.g., a C-5 propyne) or to the sugar (e.g., a carbohydrate modification), are also aspects of the present invention.

Where appropriate, the antisense nucleotide may be administered in the form of their pharmaceutically acceptable salts or as a mixture. Anti-sense oligonucleotides may be of any suitable length, e.g., from about 7 to 60 nucleotide in length, depending on the particular target being bound and their mode of delivery. Preferably the antisense oligonucleotide is directed to a gene or mRNA region containing a junction between intron and exon. Where the anti-sense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the

junction to inhibit the splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, e.g., with the 3' or 5' terminus of the antisense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotide of the intron/exon junction. Also preferred are anti-sense oligonucleotides which overlap the initiation codon. When practicing the present invention, the antisense oligonucleotides administered may be related in origin to the species to which it is administered. When treating humans, the anti-sense may be derived from human sequences. However, sequences obtained from one species are also suitable for administration to a second species.

The pharmaceutical compositions provided herein comprise the anti-sense oligos given above. Optionally, the pharmaceutical compositions may also comprise one or more surfactants. Suitable surfactants or surfactant components for enhancing the uptake of the anti-sense oligonucleotides of the invention include synthetic and natural as well as full and truncated forms of surfactant protein A, surfactant protein B, surfactant protein C, surfactant protein D and surfactant Protein E, di-saturated phosphatidylcholine (other than dipalmitoyl), dipalmitoylphosphatidylcholine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylethanolamine, phosphatidylserine; phosphatidic acid, ubiquinones, lysophosphatidylethanolamine, lysophosphatidylcholine, palmitoyllysophosphatidylcholine, dehydroepiandrosterone, dolichols, sulfatidic acid, glycerol-3-phosphate, dihydroxyacetone phosphate, glycerol, glycero-3-phosphocholine, dihydroxyacetone, palmitate, cytidine diphosphate (CDP) diacylglycerol, CDP choline, choline, choline phosphate; as well as natural and artificial lamelar bodies which are the natural carrier vehicles for the components of surfactant, omega-3 fatty acids, polyenic acid, polyenoic acid, lecithin, palmitinic acid, non-ionic block copolymers of ethylene or propylene oxides, polyoxypropylene, monomeric and polymeric, polyoxyethylene, monomeric and polymeric, poly (vinyl amine) with dextran and/or alkanoyl side chains, Brij 35, Triton X-100 and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone, among others. These surfactants may be used either as single or part of a multiple component surfactant in a formulation, or as covalently bound additions to the 5' and/or 3' ends ofthe anti-sense oligonucleotides (oligos). These compositions are administered in amounts effective to reduce the expression of an adenosine receptor, such as the adenosine A₁, A_{2b} or A₃ receptor by passing through a cell membrane and binding specifically with mRNA encoding an adenosine A₁, A_{2b} or A₃ receptor in the cell and prevent its translation. In addition, the present oligos and other agents in general may be targeted to the adenosine A2a receptor to activate this receptor or increase the amount present (agonist activity). Such compositions may contain a suitable pharmaceutically acceptable carrier e.g., sterile pyrogen-free saline solution, and the like. The anti-sense oligonucleotides may be formulated as topical and systemic formulations, in a variety of types, including oral, buccal, nasal, otical, rectal, inhalable, slow release, enteric coated, dermal, intradermal, injectable, and many more as is known in the art. The formulation of the invention may also comprise a hydrophobic carrier capable of passing through a cell membrane, e.g., in a liposome, with the liposomes carried in a pharmaceutically acceptable aqueous carrier. The oligonucleotides may also be coupled to a substance which inactivates mRNA, such as a ribozyme. The present oligonucleotides may be administered to a subject afficted with any disease or condition associated with the lung adenosine receptors to inhibit the activation of A₁ or A₃ adenosine receptors. The pharmaceutical formulation may also contain chimeric molecules comprising antisense oligonucleotides attached to molecules which are known to be internalized by cells. These oligonucleotide conjugates utilize cellular uptake pathways to

increase the cellular concentrations of oligonucleotides. Examples of macromolecules used in this manner include transferrin, asialoglycoprotein (bound to oligonucleotides via polylysine or other chemical linkages) and streptavidin.

In the pharmaceutical formulation, the anti-sense compound may be contained within a lipid particle or vesicle, such as a liposome or microcrystal. The lipid particles may be of any suitable structure, such as unilamellar or plurilamellar, so long as the antisense oligonucleotide is contained therein. Positively charged lipids such as N- [1-(2, 3 -dioleoyloxi) propyl] -N, N, N-trimethyl-ammoniumethylsulfate, or "DOTAP," are particularly preferred for such particles and vesicles. The preparation of such lipid particles is well known. See, e.g. U.S. Patent Nos. 4,880,635 to Janoff et al.; 4,906,477 to Kurono et al.; 4,911,928 to Wallach; 4,917,951 to Wallach; 4,920,016 to Allen et al.; 4,921,757 to Wheatley et al.; etc.

The composition of the invention may be administered by any means which transports the antisense nucleotide composition to the lung. The antisense compounds disclosed herein may be administered to the lungs of a patient by any suitable means, but are preferably administered by inhalation of an aerosol comprised of respirable particles which comprise the anti-sense compound. The respirable particles may be liquid or solid, and they may optionally contain other therapeutic or diagnostic ingredients as well as other typical ingredients for a particular formulation. Examples of other agents are analgesics such as acetominophen, anilerdine, aspirin, buprenorphine, butabital, butorpphanol, Choline Salicylate, Codeine, Dezocine, Diclofenac, Diflunisal, Dihydrocodeine, Elcatoninin, Etodolac, Fenoprofen, Hydrocodone, Hydromorphone, Ibuprofen, Ketoprofen, Ketorolac, Levorphanol. Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Meperidine, Methadone, Methotrimeprazine, Morphine, Nalbuphine, Naproxen, Opium, Oxycodone, Oxymorphone, Pentazocine, Phenobarbital, Propoxyphene, Salsalate, Sodium Salicylate, Tramadol and Narcotic analgesics in addition to those listed above. See, Mosby's Physician's GenRx. Anti- anxiety agents are also useful including Alprazolam, Bromazepam, Buspirone, Chlordiazepoxide, Chlormezanone, Clorazepate, Diazepam, Halazepam, Hydroxyzine, Ketaszolam, Lorazepam, Meprobamate, Oxazepam and Prazepam, among others. Anti-anxiety agents associated with mental depression, such as Chlordiazepoxide, Amitriptyline, Loxapine Maprotiline and Perphenazine, among others. Anti-inflammatory agents such as non-rheumatic Aspirin, Choline Salicylate, Diclofenac, Diflunisal, Etodolac, Fenoprofen, Floctafenine, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Magnesium Salicylate, Meclofenamate, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Phenylbutazone, Piroxicam, Salsalate, Sodium Salicylate, Sulindac, Tenoxicam, Tiaprofenic Acid, Tolmetin, anti-inflammatories for ocular treatment such as Diclofenac. Flurbiprofen, Indomethacin, Ketorolac, Rimexolone (generally for post-operative treatment), anti-inflammatories for, non-infectious nasal applications such as Beclomethaxone, Budesonide. Dexamethasone, Flunisolide, Triamcinolone, and the like. Soporifics (anti-insomnia/sleep inducing agents) such as those utilized for treatment of insomnia, including Alprazolam, Bromazepam, Diazepam, Diphenhydramine, Doxylamine, Estazolam, Flurazepam, Halazepam, Ketazolam, Lorazepam. Nitrazepam, Prazepam Quazepam, Temazepam, Triazolam, Zolpidem and Sopiclone, among others. Sedatives including Diphenhydramine, Hydroxyzine, Methotrimeprazine, Promethazine, Propofol. Melatonin, Trimeprazine, and the like. Sedatives and agents used for treatment of petit mal and tremors. among other conditions, such as Amitriptyline HCl; Chlordiazepoxide, Amobarbital; Secobarbital, Aprobarbital, Butabarbital, Ethchiorvynol, Glutethimide, L-Tryptophan, Mephobarbital, MethoHexital

Na, Midazolam Hcl, Oxazepam, Pentobarbital Na, Phenobarbital, Secobarbital Na, Thiamylal Na, and many others. Agents used in the treatment of head trauma (Brain Injury/Ischemia), such as Enadoline HCl (e.g. for treatment of severe head injury; orphan status, Warner Lambert), cytoprotective agents, and agents for the treatment of menopause, menopausal symptoms (treatment), e.g. Ergotamine, Belladonna Alkaloids and Phenobarbital, for the treatment of menopausal vasomotor symptoms, e.g. Clonidine, Conjugated Estrogens and Medroxyprogesterone, Estradiol, Estradiol Cypionate, Estradiol Valerate, Estrogens, conjugated Estrogens, esterified Estrone, Estropipate, and Ethinyl Estradiol. Examples of agents for treatment of pre menstrual syndrome (PMS) are Progesterone, Progestin, Gonadotrophic Releasing Hormone, Oral contraceptives, Danazol, Luprolide Acetate, Vitamin B6. Examples of agents for treatment of emotional/psychiatric treatments such as Tricyclic Antidepressants, including Amitriptyline HCl (Elavil), Amitriptyline HCl, Perphenazine (Triavil) and Doxepin HCl (Sinequan). Examples of tranquilizers, anti-depressants and anti-anxiety agents are Diazepam (Valium), Lorazepam (Ativan), Alprazolam (Xanax), SSRI's (selective Ssrotonin reuptake inhibitors), Fluoxetine HCl (Prozac), Sertaline HCl (Zoloft), Paroxetine HCl (Paxil), Fluvoxamine Maleate (Luvox), Venlafaxine HCl (Effexor), Serotonin, Serotonin Agonists (Fenfluramine), and other over the counter (OTC) medications. Also suitable are heart medicines, renal agents, and the like, which are known in the art.

The anti-sense compound may be administered in an anti-cardiac, anti-cardiopulmonary and/or anti-renal damage or failure effective amount which depends upon the disease being treated, the condition of the subject, the particular formulation, the route of administration, the timing of administration to a subject, etc. In general, intracellular concentrations of the oligonucleotide of from about 0.05 to about 50 µM, or more particularly about 0.2 to about 5 µM, are desirable. For administration to a subject such as a human, a dosage of about 0.01, 0.1, or 1 mg/Kg up to about 50, 100, or 150 mg/Kg or more is typically employed. However, other doses are also contemplated in this patent, particularly when varying the route of administration. Depending on the solubility of the active compound in any particular formulation, the daily dose may be divided among one or several unit dose administrations. The administration of the anti-sense compound may be carried out therapeutically, i.e., as a rescue treatment, or prophylactically, alone or in conjunction with other therapeutic or diagnostic agents as described above.

The anti-sense compound of the present invention is preferably administered into the respiratory system, e.g. by inhalation, nasal spraying, or generally into the lungs, as a formulation including particles of respirable size, e.g. particles of a size sufficiently small to pass through the nose, mouth and larynx upon inhalation and through the bronchi and alveoli of the lungs. In general, respirable particles range from about 0.5 to 10 microns in size. Particles of non-respirable size which are included in, for example, an aerosol tend to deposit in the throat and be swallowed, and the quantity of non-respirable particles in the aerosol is thus minimized. For nasal administration, a particle size in the range of about 10-500 µm is preferred to ensure retention in the nasal cavity. Other sizes, however, are also suitable as are other routes of administration.

Liquid pharmaceutical compositions of active compound for producing an aerosol may be prepared by combining the antisense compound with a suitable vehicle, such as sterile pyrogen free water. Other therapeutic compounds may optionally be included.

Solid particulate compositions containing respirable dry particles of micronized antisense compound may be prepared by grinding dry antisense compound with a mortar and pestle, and then

passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising of the antisense compound may optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which may be blended with the antisense compound in any suitable ratio, e.g., a 1 to 1 ratio by weight.

The aerosols of liquid particles comprising the antisense compound may be produced by any suitable means, such as with a nebulizer. See, e.g., U.S. Patent No. 4,501,729. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, antioxidants, flavoring agents, volatile oils, buffering agents and surfactants.

The aerosols of solid particles comprising the active compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150 µl, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute, more preferably from about 30 to 150 liters per minute, and most preferably about 60 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly.

The following examples are provided to illustrate the present invention, and should not be

construed as limiting thereon. In these examples,  $\mu$ M means micromolar, mL means milliliters,  $\mu$ m means micrometers, mm means millimeters, cm means centimeters, °C means degrees Celsius,  $\mu$ g means micrograms, mg means milligrams, g means grams, kg means kilograms, M means molar, and h means hours.

#### **EXAMPLES**

# Example 1: Design and Synthesis of Anti-sense Oligonucleotides & Controls

The design of anti-sense oligonucleotides against the adenosine receptors is based on the primary and secondary structure of the target receptor mRNA. The anti-sense oligonucleotide are selected, and optimally modified, to target regions of mRNA which confer functional activity or stability to the mRNA and which preferably may overlap the initiation codon. For instance, regions that afford particularly strong binding, such as CG strings are preferred, i.e. runs of G and/or C preferably at the 5'-end of the target region within the target gene or mRNA. However, other target sites within the molecule are suitable as well, particularly those which have low sequence overlapping with other gene sequences, thus increasing the specificity of the treatment.

Other oligonucleotides not totally complementary to the target mRNA, but containing identical nucleotide compositions on a w/w basis (controls), are included as controls in anti-sense experiments to demonstrate the specificity of the activity of the agents of this invention.

The primary and secondary structure of the human adenosine A₁ receptor mRNA was analyzed and used as described above to design anti-sense oligonucleotides, including the ones, whose sequences are provided. One anti-sense oligonucleotide (Oligo I) was synthesized as a phosphorothioate, designated HAdAlAS, and has the following sequence:

#### 5' -GAT GGA GGG CGG CAT GGC GGG-3' (SEQ ID NO:1)

As a control, a mis-matched phosphorothioate anti-sense nucleotide designated HAdAlMM was synthesized with the following sequence.

### 5' -GTA GCA GGC GGG GAT GGG GGC-3' (SEQ ID NO:2)

The oligonucleotides of SEQ. ID NOS: 1 and 2 shown above have identical base contents and general sequence structures. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligonucleotide was specific for the human and rabbit adenosine A₁ receptor genes, and that the mis-matched control was not a candidate for hybridization with any known gene sequence.

In the same manner, the primary and secondary structure of the human adenosine A₃ receptor mRNA was analyzed and various oligos selected, and the following two synthesized as phosphorothioate anti-sense oligonucleotides. The first anti-sense oligonucleotide (HAdA3AS1) synthesized has the following sequence: 5'-GTT GTT GGG CAT CTT GCC-3' (SEQ ID NO:3). As a control, a mis-matched phosphorothioate anti-sense oligonucleotide (HAdA3MM1) was synthesized, which has the following sequence: 5'-GTA CTT GCG GAT CTA GGC-3' (SEQ ID NO:4). The second phosphorothioate anti-sense oligonucleotide (HadA3AS2) has the following sequence: 5'-GTG GGC CTA GCT CTC GCC-3' (SEQ ID NO:5). As a control, its mis-matched oligonucleotide (HAdA3MM2) has the following sequence: 5'-GTC GGG GTA CCT GTC GGC-3' (SEQ ID NO:6).

All phosphorothicate oligonucleotides were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, MD).

# Example 2: In Vitro Testing of A₁-Adenosine Receptor Anti-sense Oligonucleotides

The anti-sense oligonucleotide against the human  $A_1$  receptor (SEQ ID NO:1) described above was tested for efficacy in an in vitro model utilizing lung adenocarcinoma cells HTB-54. HTB-54 lung adenocarcinoma cells were demonstrated to express the  $A_1$  adenosine receptor using standard northern blotting procedures and receptor probes designed and synthesized in the laboratory.

HTB-54 human lung adenocarcinoma cells (106/100 mm tissue culture dish) were exposed to 5.0 μM HAdAlAS or HAdAlMM for 24 hours, with a fresh change of media and oligonucleotides after 12 hours of incubation. Following 24 hour exposure to the oligonucleotides, cells were harvested and their RNA extracted by standard procedures. A 21-mer probe corresponding to the region of mRNA targeted by the anti-sense (and therefore having the same sequence as the anti-sense, but not phosphorothioated) was synthesized and used to probe northern blots of RNA prepared from HAdAlAS-treated, HAdAlMM-treated and non-treated HTB-54 cells. These blots showed clearly that HAdAlAS but not HAdAlMM effectively reduced human adenosine receptor mRNA by >50%. This result showed that HAdAlAS is a good candidate for an anti-asthma drug since it depletes intracellular mRNA for the adenosine A₁ receptor, which is involved in asthma.

# Example 3: In Vivo Efficacy of A₁ Adenosine Receptor Anti-sense Oligonucleotides

A fortuitous homology between the rabbit and human DNA sequences within the adenosine  $A_1$  gene overlapping the initiation codon permitted the use of the phosphorothicate anti-sense oligonucleotides initially designed for use against the human adenosine  $A_1$  receptor in a rabbit model.

Neonatal New Zealand white Pasteurella-free rabbits were immunized intraperitoneally within 24 hours of birth with 312 antigen units/mL house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA), mixed with 10% kaolin. Immunizations were repeated weekly for the first month and then biweekly for the next 2 months. At 3-4 months of age, eight sensitized rabbits were anesthetized and relaxed with a mixture of ketamine hydrochloride (44 mg/kg) and acepromazine maleate (0.4 mg/kg) administered intramuscularly.

The rabbits were then laid supine in a comfortable position on a small molded, padded animal board and intubated with a 4.0-mm intratracheal tube (Mallinkrodt, Inc., Glens Falls, NY). A polyethylene catheter of external diameter 2.4 mm with an attached latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiments. The intratracheal tube was attached to a heated Fleisch pneumotachograph (size 00; DOM Medical, Richmond, VA), and flow was measured using a Validyne differential pressure transducer (Model DP-45161927; Validyne Engineering Corp., Northridge, CA) driven by a Gould carrier amplifier (Model 11-4113; Gould Electronic, Cleveland, OH). The esophageal balloon was attached to one side of the differential pressure transducer, and the outflow of the intratracheal tube was connected to the opposite side of the pressure transducer to allow recording of transpulmonary pressure. Flow was integrated to give a continuous tidal volume, and measurements of total lung resistance (RL) and dynamic compliance (Cdyn) were calculated at isovolumetric and flow zero points, respectively, using an automated respiratory analyzer (Model 6; Buxco, Sharon, CT).

Animals were randomized and on Day 1 pretreatment values for PC50 were obtained for

aerosolized adenosine. Anti-sense (HAdAlAS) or mismatched control (HAdAlMM) oligonucleotides were dissolved in sterile physiological saline at a concentration of 5000  $\mu g$  (5 mg) per 1.0 ml. Animals were subsequently administered the aerosolized anti-sense or mismatch oligonucleotide via the intratracheal tube (approximately 5000  $\mu g$  in a volume of 1.0 ml), twice daily for two days. Aerosols of either saline, adenosine, or anti-sense or mismatch oligonucleotides were generated by an ultrasonic nebulizer (DeVilbiss, Somerset, PA), producing aerosol droplets 80% of which were smaller than 5  $\mu m$  in diameter.

In the first arm of the experiment, four randomly selected allergic rabbits were administered antisense oligonucleotide and four the mismatched control oligonucleotide. On the morning of the third day, PC50 values (the concentration of aerosolized adenosine in mg/ml required to reduce the dynamic compliance of the bronchial airway 50% from the baseline value) were obtained and compared to PC50 values obtained for these animals prior to exposure to oligonucleotide.

Following a 1 week interval, animals were crossed over, with those previously administered mismatch control oligonucleotide now administered anti-sense oligonucleotide, and those previously treated with anti-sense oligonucleotide now administered mismatch control oligonucleotide. Treatment methods and measurements were identical to those employed in the first arm of the experiment. It should be noted that in six of the eight animals treated with anti-sense oligonucleotide, adenosine-mediated bronchoconstriction could not be obtained up to the limit of solubility of adenosine, 20 mg/ml. For the purpose of calculation, PC50 values for these animals were set at 20 mg/ml. The values given therefore represent a minimum figure for anti-sense effectiveness. Actual effectiveness was higher. The results of this experiment are illustrated in both Figure 1 and Table 1.

<u>Table 1</u>: Adenosine A₁ Receptor Anti-sense Oligonucleotide Effect upon PC50 Values in Asthmatic Rabbits

Mismatch Control		A ₁ Receptor Anti-sense Oligonucleotide		
Pre-oligonucleotide	Post-oligonucleotide	Pre-oligonucleotide	Post-oligonucleotide	
3.56 ± 1.02	5.16 ± 1.93	2.36 ± 0.68	>19.5 ± 0.34**	

Results are presented as the mean (n=8)"SEM. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected t test. **Significantly different from all other groups, P < 0.01.

In both arms of the experiment, animals receiving the anti-sense oligonucleotide showed an order of magnitude increase in the dose of aerosolized adenosine required to reduce dynamic compliance of the lung by 50%. No effect of the mismatched control oligonucleotide upon PC50 values was observed. No toxicity was observed in any animal receiving either anti-sense or control inhaled oligonucleotide.

These results show clearly that the lung has exceptional potential as a target for anti-sense oligonucleotide-based therapeutic intervention in lung disease. They further show, in a model system which closely resembles human asthma, that down regulation of the adenosine A₁ receptor largely eliminates adenosine-mediated bronchoconstriction in asthmatic airways. Bronchial hyper-responsiveness in the allergic rabbit model of human asthma is an excellent endpoint for anti-sense intervention since the tissues involved in this response lie near to the point of contact with aerosolized oligonucleotides, and the model closely simulates an important human disease.

## Example 4: Specificity of A1-adenosine Receptor Anti-sense Oligonucleotide

At the conclusion of the crossover experiment of Example 3, airway smooth muscle from all rabbits was quantitatively analyzed for adenosine  $A_1$  receptor number. As a control for the specificity of the anti-sense oligonucleotide, adenosine  $A_2$  receptors, which should not have been affected, were also quantified.

Airway smooth muscle tissue was dissected from each rabbit and a membrane fraction prepared according to described methods (Kleinstein, J., and Glossmann, H., Naunyn-Schmiedeberg's Arch. Pharmacol. 305, 191-200 (1978), with slight modifications. Crude plasma membrane preparations were stored at -70°C until the time of assay. Protein content was determined by the method of Bradford (M. Bradford, Anal. Biochem. 72, 240-254 (1976)). Frozen plasma membranes were thawed at room temperature and were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. The binding of [³H] DPCPX (A₁ receptor-specific) or [³H] CGS-21680 (A₂ receptor-specific) was measured as previously described. See, Ali, S., et al., J. Pharmacol. Exp. Ther. 268, 1328-1334 (1994); S. Ali et al., Am. J. Physiol. 266, L271-277 (1994).

As illustrated in both Figure 2 and Table 2, animals treated with adenosine  $A_1$  anti-sense oligonucleotide in the crossover experiment had a nearly 75% decrease in  $A_1$  receptor number compared to controls, as assayed by specific binding of the  $A_1$ -specific antagonist DPCPX. There was no change in adenosine  $A_2$  receptor number, as assayed by specific binding of the  $A_2$  receptor-specific agonist 2- [p-(2-carboxyethyl)-phenethylamino] -5'-(N-ethylcarboxamido) adenosine (CGS-21680).

<u>Table 2</u>: Specificity or Action of Adenosine A Receptor Anti-sense Oligonucleotide

	Mismatch Control Oligonucleotide	A ₁ -Anti-sense Oligonucleotide
	(Mean ± SD) n=8	(Mean <u>+</u> SD) n=8
A ₁ -Specific Binding	1,105 ± 48**	293 ± 18
A ₂ -Specific Binding	302 ± 22**	442 ± 171

Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey's protected t test. **Significantly different from mismatch control, p < 0.01.

# Example 5: In Vivo Response to Adenosine Challenge with & without Oligo I Pretreatment

Two hyper responsive monkeys (ascaris sensitive) were challenged with inhaled adenosine, with and without pre-treatment with anti-sense oligo I (SEQ.ID NO: 1). The PC₄₀ adenosine was calculated from the data collected as being equivalent to that amount of adenosine in mg that causes a 40% decrease in dynamic compliance in hyper-responsive airways.

The Oligo I (SEQ. ID NO:1; EPI 2010) was subsequently administered at 10 mg/day for 2 days by inhalation. On the third day, PC adenosine was again measured. The results are shown in Figure 3 accompanying this patent. The left bar shows the PC₄₀ adenosine value prior to treatment with Oligo I whereas the right bar shows the PC₄₀ adenosine taken after administration of Oligo I. As can be seen in Figure 3, any sensitivity to adenosine was completely eliminated by the administration of the oligo of this invention in one animal, and substantially reduced in the second.

#### **Example 6:** Anti-sense Oligos directed to other Target Nucleic Acids

This work was conducted to demonstrate that the present invention is broadly applicable to antisense oligonucleotides ("oligos") specific to nucleic acid targets broadly. The following experimental studies were conducted to show that the method of the invention is broadly suitable for use with antisense oligos designed as taught by this application and targeted to any and all adenosine receptor mRNAs. For this purpose, various anti-sense oligos were prepared to adenosine receptor mRNAs exemplified by the adenosine  $A_1$ ,  $A_{2b}$  and  $A_3$  receptor mRNAs.

Anti-sense Oligo I was disclosed above (SEQ. ID NO: 1). Five additional anti-sense phosphorothioate oligos were designed asnd synthesized as indicated above.

- 1- Oligo II (SEQ. ID NO: 997) also targeted to the adenosine A₁ receptor, but to a different region than Oligo I.
  - 2-Oligo V (SEQ. ID NO: 1000) targeted to the adenosine A_{2b} receptor.
- 3- Oligos III (SEQ. ID NO: 998) and IV (SEQ. ID NO: 999) targeted to different regions of the adenosine A₃ receptor.
  - 4- Oligo I-PD (SEQ. ID NO:1)(a phosphodiester oligo of the same sequence as Oligo I).

These anti-sense oligos were designed for therapy on a selected species as described above and are generally specific for that species, unless the segment of the target mRNA of other species happens to contain a similar sequences. All anti-sense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and allergy, which have breathing difficulties

and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

### Example 7: Design & Sequences of other Anti-sense Oligos

Six oligos and their effects in Sa rabbit model were studied and the results of these studies are reported and discussed below. Five of these oligos were selected for this study to complement the data on Oligo I (SEQ ID NO: 1) provided in Examples 1 to 4 above. This oligo is anti-sense to one region of the adenosine A₁ receptor mRNA.

The oligos tested are identified as anti-sense Oligos I (SEQ ID NO: 1) and II (SEQ. ID No: 997) targeted to a different region of the adenosine A₁ receptor mRNA, Oligo V (SEQ. ID No: 998) targeted to the adenosine A_{2b} receptor mRNA, and anti-sense Oligos III and IV (SEQ. ID NOS: 999 and 1000) targeted to two different regions of the adenosine A₃ receptor mRNA. The sixth oligo (Oligo I-PD) is a phosphodiester version of Oligo I (SEQ. ID NO: 1). The design and synthesis of these anti-sense oligos was performed in accordance with Example 1 above.

## (I) Anti-sense Oligo I

The anti-sense oligonucleotide I referred to in Examples 1 to 5 above is targeted to the human A₁ adenosine receptor mRNA (EPI 2010). Anti-sense oligo I is 21 nucleotide long, overlaps the initiation codon, and has the following sequence: 5'-GAT GGA GGG CGG CAT GGC GGG -3' (SEQ. ID No:1)

The oligo I was previously shown to abrogate the adenosine-induced bronchoconstriction in allergic rabbits, and to reduce allergen-induced airway obstruction and bronchial hyperresponsiveness (BHR), as discussed above and shown by Nyce, J. W. & Metzger, W. J., Nature, 385:721 (1977), the relevant portions of which reference are incorporated in their entireties herein by reference.

#### (II) Anti-sense Oligo II

A phosphorothioate anti-sense oligo (SEQ. ID NO:997) was designed in accordance with the invention to target the rabbit adenosine  $A_1$  receptor mRNA region +936 to +956 relative to the initiation codon (start site). The anti-sense oligo II is 21 nucleotide long, and has the following sequence:

# 5'-CTC GTC GCC GTC GCC GGC GGG-3' (SEQ. ID NO:997)

### (III) Anti-sense Oligo III

A phosphorothioate anti-sense oligo other than that provided in Example 1 above (SEQ. ID NO:998) was designed in accordance with the invention to target the anti-sense A₃ receptor mRNA region +3 to + 22 relative to the initiation codon start site. The anti-sense oligo III is 20 nucleotide long, and has the following sequence: 5'-GGG TGC TGT TGT CGG GC-3' (SEQ. ID NO:998)

#### (IV) Anti-sense Oligo IV

Yet another phosphorothioate anti-sense oligo (SEQ. ID NO:999) was designed in accordance with the invention to target the adenosine A₃ receptor mRNA region + 386 to + 401 relative to the initiation codon (start site). The anti-sense oligo IV is 15 nucleotide long, and has the following sequence: 5'-GGC CCA GGG CCA GCC-3' (SEQ. ID NO:999)

#### (V) Anti-sense Oligo V

A phosphorothioate anti-sense oligo (SEQ. ID NO:1000) was designed in accordance with the invention to target the adenosine  $A_{2b}$  receptor mRNA region -21 to -1 relative to the initiation codon

(start site). The anti-sense oligonucleotide V is 21 nucleotide long, and has the following sequence:

5'-GGC CGG GCC AGC CGG GCC CGG-3' (SEQ. ID NO:1000)

### (VI) A₁ Mismatch Oligos

Two different mismatched oligonucleotides having the following sequences were used as controls for anti-sense oligo I (SEQ. ID NO: 1) described in Example 6 above.

A₁ MM2 5'-GTA GGT GGC GGG CAA GGC GGG-3' (SEQ. ID NO:1002)

A, MM3 5'-GAT GGA GGC GGG CAT GGC GGG-3' (SEQ. ID NO:1003)

Anti-sense oligo I and the two mismatch anti-sense oligos had identical base content and general sequence structure. Homology searches in GENBANK (release 85.0) and EMBL (release 40.0) indicated that the anti-sense oligo I was specific, not only for the human, but also for the rabbit, adenosine A₁ receptor genes, and that the mismatched controls were not candidates for hybridization with any known human or animal gene sequence.

### (VII) Anti-sense Oligo A₁-PD (Oligo VI)

A phosphodiester anti-sense oligo (Oligo VI; SEQ. ID NO:1004) having the same nucleotide sequence as Oligo I was designed as disclosed in the above-identified application. Anti-sense oligo I-PD is 21 nucleotide long, overlaps the initiation codon, and has the following sequence:

### 5'- GAT GGA GGG CGG CAT GGC GGG -3' (SEQ. ID NO:1004)

#### VIII) Controls

Each rabbit was administered 5.0 ml aerosolized sterile saline following the same schedule as for the anti-sense oligos in (II), (III), and (IV) above.

#### **Example 8:** Synthesis of Anti-sense Oligos

Phosphorothioate anti-sense oligos having the sequences described in (a) above, were synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis. Anti-sense oligonucleotide II (SEQ. ID NO:997), anti-sense oligonucleotide III (SEQ. ID NO: 998) and anti-sense oligonucleotide IV (SEQ. ID NO: 999) were each synthesized and purified in this manner.

#### **Example 9:** Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp. 347-362, CRC Press, Boca Raton (1990); Ali, S., Metzger, W. J. and Mustafa, S. J., Am. J. Resp. Crit. Care Med. 149: 908 (1994)), the relevant portions of which are incorporated in their entireties here by reference. Immunizations were repeated weekly for the first month and then biweekly until the age of 4 months. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (Ali, S., Metzger, W. J. and Mustafa,

S. J., Am. J. Resp. Crit. Care Med. 149 (1994)), the relevant section being incorporated in its entirety here by reference.

#### **DOSE-RESPONSE STUDIES**

#### Example 10: Experimental Setup

Aerosols of either adenosine (0-20 mg/ml), or anti-sense or one of two mismatch oligonucleotides (5 mg/ml) were separately prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5µm in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube.

The animals were randomized, and administered aerosolized adenosine. Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC₅₀ Adenosine). The animals were then administered either the aerosolized anti-sense or one of the mismatch anti-sense oligos via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC₅₀ values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in Example 21 below.

### **Example 11:** Crossover Experiments

For some experiments utilizing anti-sense oligo I (SEQ. ID NO:1) and a corresponding mismatch control oligonucleotide A1MM2, following a 2 week interval, the animals were crossed over, with those previously administered the mismatch control A₁MM2, now receiving the anti-sense oligo I, and those previously treated with the anti-sense oligo I, now receiving the mismatch control A₁MM2 oligo.

The number of animals per group was as follows. For mismatch  $A_1MM2$  (Control 1), n=7, since one animal was lost in the second control arm of the experiment due to technical difficulties, for mismatch  $A_1MM3$  n=4 (Control 2) and for  $A_1AS$  anti-sense oligo I, n=8. The  $A_1MM3$  oligo-treated animals were analyzed separately and were not part of the cross-over experiment. The treatment methods and measurements employed following the cross-over were identical to those employed in the first arm of the experiment.

In 6 of the 8 animals treated with the anti-sense oligo I (SEQ. ID NO:1), no PC50 value could be obtained for adenosine doses of up to 20 mg/ml, which is the limit of solubility of adenosine. Accordingly, the PC50 values for these animals were assumed to be 20 mg/ml for calculation purposes. The values given, therefore, represent a minimum figure for the effectiveness of the anti-sense oligonucleotides of the invention. Other groups of allergic rabbits (n=4 for each group) were administered 0.5 or 0.05 mg doses of the anti-sense oligo I (SEQ ID NO:1), or the A₁MM2 oligo in the manner and according to the schedule described above (the total doses being 2.0 or 0.2 mg). The results of these studies are provided in Example 23 below.

### Example 12: Anti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I (SEQ. ID NO:1) in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

The results obtained for anti-sense oligo I and its mismatch controls confirmed that the mismatch controls are equivalent to saline, as described in Example 20 below and in Table 1 of Nyce & Metzger, Nature 385, 721-725 (1997). Because of this finding, saline was used as a control for pulmonary function studies employing anti-sense oligos II, III and IV (SEQ. ID NOS: 997, 998 and 999).

# Example 13: Specificity of Oligo I for Adenosine A₁ Receptor (Receptor Binding Studies)

Tissue from airway smooth muscle was dissected to primary, secondary and tertiary bronchi from rabbits which had been administered 20 mg oligo I (SEQ. ID NO:1) in 4 divided doses over a period of 48 hours as described above. A membrane fraction was prepared according to the method of Ali et al. (Ali, S., et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994), the relevant section relating to the preparation of the membrane fraction is incorporated in its entirety hereby by reference).

The protein content was determined by the method of Bradford and plasma membranes were incubated with 0.2 U/ml adenosine deaminase for 30 minutes at 37°C to remove endogenous adenosine. See, Bradford, M. M. Anal. Biochem. 72, 240-254 (1976), the relevant portion of which is hereby incorporated in its entirety by reference. The binding of [3H]DPCPX, [3H]NPC17731, or [3H]CGS-21680 was measured as described by Jarvis et al. See, Jarvis, M.F., et al., Pharmacol. Exptl. Ther. 251, 888-893 (1989), the relevant portion of which is fully incorporated herein by reference. The results of this study are shown in Table 8 and discussed in Example 21below.

# Example 14: Pulmonary Function Measurements (Compliance cpyn and Resistance)

At 4 months of age, the immunized animals were anesthetized and relaxed with 1.5 ml of a mixture of ketamine HCl (35 mg/kg) and acepromazine maleate (1.5 mg/kg) administered intramuscularly. After induction of anesthesia, allergic rabbits were comfortably positioned supine on a soft molded animal board. Salve was applied to the eyes to prevent drying, and they were closed. The animals were then intubated with a 4.0 mm intermediate high-low cuffed Murphy 1 endotracheal tube (Mallinckrodt, Glen Falls, NY), as previously described by Zavala and Rhodes. See, Zavala and Rhodes, Proc. Soc. Exp. Biol. Med. 144: 509-512 (1973), the relevant portion of which is incorporated herein by reference in its entirety. A polyethylene catheter of OD 2.4 mm (Becton Dickinson, Clay Adams, Parsippany NJ) with an attached thin-walled latex balloon was passed into the esophagus and maintained at the same distance (approximately 16 cm) from the mouth throughout the experiment. The endotracheal tube was attached to a heated Fleisch pneumotach (size 00; DEM Medical, Richmond, VA), and the flow (v) measured using a Validyne differential pressure transducer (Model DP-45-16-1927, Validyne Engineering, Northridge, CA), driven by a Gould carrier amplifier (Model 11-4113, Gould Electronics, Cleveland, OH).

An esophageal balloon was attached to one side of the Validyne differential pressure transducer, and the other side was attached to the outflow of the endotracheal tube to obtain transpulmonary pressure  $(P_{tp})$ . The flow was integrated to yield a continuous tidal volume, and the measurements of total lung resistance  $(R_t)$  and dynamic compliance  $(C_{dyn})$  were made at isovolumetric and zero flow points. The flow, volume and pressure were recorded on an eight channel Gould 2000 W high-frequency recorder and  $C_{dyn}$  was calculated using the total volume and the difference in  $P_{tp}$  at zero flow, and .  $R_t$  was calculated as the ratio of  $P_{tp}$  and V at midtidal lung volumes. These calculations were made automatically with the Buxco automated pulmonary mechanics respiratory analyzer (Model 6, Buxco

Electronics, Sharon, CT), as previously described by Giles et al. See, Giles et al., Arch. Int. Pharmacodyn. Ther. 194: 213-232 (1971), the relevant portion of which describing these calculations is incorporated in toto hereby by reference. The results obtained upon administration of oligo II on allergic rabbits are shown and discussed in Example 27 below.

### Example 15: Measurement of Bronchial Hyperresponsiveness (BHR)

Each allergic rabbit was administered histamine by aerosol to determine their baseline hyperresponsiveness. Aerosols of either saline or histamine were generated using a DeVilbiss nebulizer (DeVilbiss, Somerset, PA) for 30 seconds and then for 2 minutes at each dose employed. The ultrasonic nebulizer produced aerosol droplets of which 80% were <5 micron in diameter. The histamine aerosol was administered in increasing concentrations (0.156 to 80 mg/ml) and measurements of pulmonary function were made after each dose. The B4R was then determined by calculating the concentration of histamine (mg/ml) required to reduce the C_{dyn} 50% from baseline (PC50 Histamine).

#### Example 16: Cardiovascular Effect of Anti-sense Oligo I

The measurement of cardiac output and other cardiovascular parameters using CardiomaxTM utilizes the principal of thermal dilution in which the change in temperature of the blood exiting the heart after a venous injection of a known volume of cool saline is monitored. A single rapid injection of cool saline was made into the right atrium via cannulation of the right jugular vein, and the corresponding changes in temperature of the mixed injectate and blood in the aortic arch were recorded via cannulation of the carotid artery by a temperature-sensing miniprobe.

Twelve hours after the allergic rabbits had been treated with aerosols of oligo I (EPI 2010; SEQ. ID NO: 1) as described in (d) above, the animals were anesthetized with 0.3 ml/kg of 80% Ketamine and 20% Xylazine. This time point coincides with previous data showing efficacy for SEQ. ID NO: 1, as is clearly shown by Nyce & Metzger, (1997), supra, the pertinent disclosure being incorporated in its entirety here by reference. A thermocouple was then inserted into the left carotid artery of each rabbit, and was then advanced 6.5 cm and secured with a silk ligature. The right jugular vein was then cannulated and a length of polyethylene tubing was inserted and secured.

A thermodilution curve was then established on a CardiomaxTM II (Columbus Instruments, Ohio) by injecting sterile saline at 20°C to determine the correctness of positioning of the thermocouple probe. After establishing the correctness of the position of the thermocouple, the femoral artery and vein were isolated. The femoral vein was used as a portal for drug injections, and the femoral artery for blood pressure and heart rate measurements. Once constant baseline cardiovascular parameters were established, CardiomaxTM measurements of blood pressure, heart rate, cardiac output, total peripheral resistance, and cardiac contractility were made.

# Example 17: Duration of Action of Oligo I (SEQ. ID NO: 1)

Eight allergic rabbits received initially increasing log doses of adenosine by means of a nebulizer via an intra-tracheal tube as described in (f) above, beginning with 0.156 mg/ml until compliance was reduced by 50% (PC50 Adenosine) to establish a baseline. Six of the rabbits then received four 5 mg aerosolized doses of (SEQ. ID NO:1) as described above. Two rabbits received equivalent amounts of saline vehicle as controls. Beginning 18 hours after the last treatment, the PC50 Adenosine values were tested again. After this point, the measurements were continued for all animals each day, for up to 10 days. The results of this study are discussed in Example 26 below.

# Example 18: Reduction of Adenosine A_{2b} Receptor Number by Anti-sense Oligo V

Sprague Dawley rats were administered 2.0 mg respirable anti-sense oligo V (SEQ. ID NO:1000) three times over two days using an inhalation chamber as described above. Twelve hours after the last administration, lung parenchymal tissue was dissected and assayed for adenosine  $A_{2b}$  receptor binding using [311]-NECA as described by Nyce & Metzger (1997), supra. Controls were conducted by administration of equal volumes of saline. The results are significant at p<0.05 using Student's paired t test, and are discussed in Example 29 below.

# Example 19: Comparison of Oligo I & Corresponding Phosphodiester Oligo VI (SEQ. ID NO:1004)

Oligo I (SEQ ID NO:1) countered the effects of adenosine and eliminated sensitivity to it for adenosine amounte up to 20 mg adenosine/5.0 ml (the limit of solubility of adenosine). Oligo VI (SEQ. ID NO:1004), the phosphodiester version of the oligonucleotide sequence, was completely ineffective when tested in the same manner. Both compounds have identical sequence, differing only in the presence of phosphorothioate residues in Oligo I (SEQ ID NO:1), and were delivered as an aerosol as described above and in Nyce & Metzger (1997), supra. Significantly different at p<0.001, Student's paired t test. The results are discussed in Example 30 below.

#### **RESULTS OBTAINED FOR ANTI-SENSE OLIGO I (SEQ. ID NO: 1)**

### Example 20: Results of Prior Work

The nucleotide sequence and other data for anti-sense oligo I (SEQ. ID NO:1), which is specific for the adenosine  $A_1$  receptor, were provided above. The experimental data showing the effectiveness of oligo I in down regulating the receptor number and activity were also provided above.

Further information on the characteristics and activities of anti-sense oligo I is provided in Nyce, J. W. and Metzger, W. J., Nature 385:721 (1997), the relevant parts of which relating to the following results are incorporated in their entireties herein by reference. The Nyce & Metzger (1997) publication provided data showing that the anti-sense oligo I (SEQ. ID NO:1):

- (1) The anti-sense oligo I reduces the number of adenosine  $A_1$  receptors in the bronchial smooth muscle of allergic rabbits in a dose-dependent manner as may be seen in Table 3 below.
- (2) Anti-sense Oligo I attenuates adenosine-induced bronchoconstriction and allergen-induced bronchoconstriction.
- (3) The Oligo I attenuates bronchial hyperresponsiveness as measured by PC₅₀ histamine, a standard measurement to assess bronchial hyperresponsiveness. This result clearly demonstrates anti-inflammatory activity of the anti-sense oligo I as is shown in Table 2 above.
- (4) As expected, because it was designed to target it, the anti-sense oligo I is totally specific for the adenosine  $A_1$  receptor, and has no effect at all at any dose on either the very closely related adenosine  $A_2$  receptor or the related bradykinin  $B_2$  receptor. This is seen in Table 3 below.
- (5) In contradistinction to the above effects of the Oligo I, the mismatch control molecules MM2 and MM3 (SEQ. ID NO:1002 and SEQ. ID NO:1003) which have identical base composition and molecular weight but differed from the anti-sense oligo I (SEQ ID NO: 1) by 6 and 2 mismatches, respectively. These mismatches, which are the minimum possible while still retaining identical base

composition, produced absolutely no effect upon any of the targeted receptors  $(A_1, A_2 \text{ or } B_2)$ .

These results, along with a complete lack of prior art on the use of anti-sense oligonucleotides, such as oligo I, targeted to the adenosine  $A_1$  receptor, are unexpected results. The showings presented in this patent clearly enable and demonstrate the effectiveness, for their intended use, of the claimed agents and method for treating a disease or condition associated with lung airway, such as bronchoconstriction, inflammation, allergy(ies), and the like.

# Example 21: Oligo I Significantly Reduces Response to Adenosine Challenge

The receptor binding experiment is described in Example 13 above, and the results shown in Table 3 below which shows the binding characteristics of the adenosine  $A_1$ -selective ligand [ $_3$ H]DPCPX and the bradykinin  $B_2$ -selective ligand [ $_3$ H]NPC 17731 in membranes isolated from airway smooth muscle of  $A_1$  adenosine receptor and  $B_2$  bradykinin receptor anti-sense- and mismatch-treated allergic rabbits.

Table 3: Binding Characteristics of Three Anti-Sense Oligos

Treatment ¹	A, receptor		B, receptor	
	Kd	$\mathbf{B}_{max}$	Kd	Bmax
Adenosine A ₁	Receptor			
20 mg	0.36±0.029 nM	19±1.52 fmoles*	0.39±0.031 nM	14.8±0.99fmoles
2 mg	0.38±0.030 nM	32±2.56 fmoles*	$0.41 \pm 0.028 \text{ nM}$	$15.5\pm1.08$ fmoles
0.2 mg	0.37±0.030 nM	49±3.43 fmoles	0.34±0.024 nM	15.0±1.06 fmoles
A ₁ MM1	(Control)			
20 mg	$0.34 \pm 0.027 \text{ nM}$	52.0±3.64 fmoles	0.35±0.024 nM	14.0±1.0 fmoles
2 mg	0.37±0.033 nM	51.8±3.88 fmoles	$0.38\pm0.028~\mathrm{nM}$	14.6±1.02 fmoles
B ₂ A (Bradykinin	Receptor)			
20 mg	0.36±0.028 nM	45.0±3.15 fmoles	0.38±0.027 nM	8.7±0.62 fmoles*
2 mg	$0.39 \pm 0.035 \text{ nM}$	44.3±2.90 fmoles	0.34±0.024 nM	11.9±0.76 fmoles**
0.2 mg	0.40±0.028 nM	47.0±3.76 fmoles	0.35±0.028 nM	15.1±1.05 fmoles
B ₂ MM (Control)				
20 mg	0.39±0.031 nM	42.0±2.94 fmoles	$0.41 \pm 0.029 \text{ nM}$	14.0±0.98 fmoles
2 mg	0.41±0.035 nM	40.0±3.20 fmoles	0.37±0.030 nM	14.8±0.99 fmoles
0.2 mg	0.37±0.029 nM	43.0±3.14 fmoles	0.36±0.025 nM	15.1±1.35 fmoles
Saline Control	0.37±0.041	46.0±5.21	0.39±0.047 nM	14.2±1.35 fmoles

Refers to total oligo administered in four equivalently divided doses over a 48 hour period. Treatments and analyses were performed as described in methods. Significance was determined by repeated-measures analysis of variance (ANOVA), and Tukey=s protected t test. N = 4-6 for all groups.

# Example 22: Dose-response Effect of Oligo I

Anti-sense oligo I (SEQ ID NO:1) was found to reduce the effect of adenosine administration to the animal in a dose-dependent manner over the dose range tested as shown in Table 4 below.

<u>Table 4</u>: Dose-Response Effect to Anti-sense Oligo I

Total Dose (mg)	PC _{50 Adenosine} (mg Adenosine)
Anti-sense Oligo I 0.2 2.0 20	8.32±7.2 14.0±7.2 19.5±0.34
A ₁ MM2 oligo (control) 0.2 2.0 20	2.51±0.46 3.13± 0.71 3.25± 0.34

The above results were studied with the Student=s paired t test and found to bestatistically different, p=0.05

Significantly different from mismatch control- and saline-treated groups, p<0.001;</li>
 **Significantly different from mismatch control- and saline-treated groups, p<0.05.</li>

The oligo I (SEQ. ID NO:1), an anti-adenosine  $A_1$  receptor oligo, acts specifically on the adenosine  $A_1$  receptor, but not on the adenosine  $A_2$  receptors. These results stem from the treatment of rabbits with anti-sense oligo I (SEQ. ID NO:1) or mismatch control oligo (SEQ. ID NO:1002;  $A_1$ MM2) as described in Example 9 above and in Nyce & Metzger (1997), supra (four doses of 5 mg spaced 8 to 12 hours apart via nebulizer via endotracheal tube), bronchial smooth muscle tissue excised and the number of adenosine  $A_1$  and adenosine  $A_2$  receptors determined as reported in Nyce & Metzger (1997), supra.

# Example 23: Specificity of Oligo I (SEQ. ID NO:1) for Target Gene Product

Oligo I (SEQ. ID No:1) is specific for the adenosine A₁ receptor whereas its mismatch controls had no activity. Figure 1 depicts the results obtained from the cross-over experiment described in Example 10 above and in Nyce & Metzger (1997), supra. The two mismatch controls (SEQ. ID NO:1002 and SEQ. ID NO:1003) evidenced no effect on the PC₅₀ Adenosine value. On the contrary, the administration of anti-sense oligo I (SEQ. ID NO:1) showed a seven-fold increase in the PC₅₀ Adenosine value. The results clearly indicate that the anti-sense oligo I (SEQ. ID NO:1) reduces the response (attenuates the sensitivity) to exogenously administered adenosine when compared with a saline control. The results provided in Table 2 above clearly establish that the effect of the anti-sense oligo I is dose dependent (see, column 3 of Table 1).

The Oligo I was also shown to be totally specific for the adenosine  $A_1$  receptor, (see, top 3 rows of Table), inducing no activity at either the closely related adenosine  $A_2$  receptor or the bradykinin  $B_2$  receptor (see, lines 8-10 of Table 2 above).

In addition, the results shown in Table 2 establish that the anti-sense oligo I (SEQ. ID NO:1) decreases sensitivity to adenosine in a dose dependent manner, and that it does this in an anti-sense oligo-dependent manner since neither of two mismatch control oligonucleotides (A₁MM2; SEQ. ID NO:1002 and A₁MM3; SEQ. ID NO:1003) show any effect on PC_{50 Adenosine} values or on attenuating the number of adenosine A₁ receptors.

# Example 24: Effect on Aeroallergen-induced Bronchoconstriction & Inflammation

The Oligo I (SEQ. ID NO:1) was shown to significantly reduce the histamine-induced effect in the rabbit model when compared to the mismatch oligos. The effect of the anti-sense Oligo I (SEQ. ID No:1) and the mismatch oligos (A₁MM2, SEQ. ID NO:1002 and A₁MM3, SEQ. ID NO:1003) on allergen-induced airway obstruction and bronchial hyperresponsiveness was assessed in allergic rabbits.

The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced airway obstruction was assessed. As calculated from the area under the plotted curve, the anti-sense oligo I significantly inhibited allergen-induced airway obstruction when compared with the mismatched control (55%, p<0.05; repeated measures ANOVA, and Tukey's t test).

A complete lack of effect was induced by the mismatch oligo A₁MM2 (Control) on allergen induced airway obstruction.

The effect of the anti-sense oligo I (SEQ. ID NO:1) on allergen-induced BHR was determined as above. As calculated from the PC_{50 Histamine} value, the anti-sense oligo I (SEQ. ID NO:1)

significantly inhibited allergen-induced BHR in allergic rabbits when compared to the mismatched control (61%, p<0.05; repeated measures ANOVA, Tukey's t test).

A complete lack of effect of the A₁MM mismatch control on allergen-induced BHR was observed.

The results indicated that anti-sense oligo I (SEQ. ID NO: 1) is effective to protect against aeroallergen-induced bronchoconstriction (house dust mite). In addition, the anti-sense oligo I (SEQ. ID NO:1) was also found to be a potent inhibitor of dust mite-induced bronchial hyper responsiveness, as shown by its effects upon histamine sensitivity which indicates anti- inflammatory activity for anti-sense oligo I (SEQ. ID NO:1).

# Example 25: Anti-sense Oligo I is Free of Deleterious Side Effects

The Oligo I (SEQ. ID NO:1) was shown to be free of side effects that might be toxic to the recipient. No changes in arterial blood pressure, cardiac output, stroke volume, heart rate, total peripheral resistance or heart contractility (dPdT) were observed following administration of 2.0 or 20 mg oligo I (SEQ. ID NO:1). The addition, the results of the measurement of cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), heart rate (HR), total peripheral resistance (TPR), and contractility (dPdT) with a Cardiomax™ apparatus (Columbus Instruments, Ohio) were assessed.

These results evidenced that oligo I (SEQ. ID NO:1) has no detrimental effect upon critical cardiovascular parameters. More particularly, this oligo does not cause hypotension. This finding is of particular importance because other phosphorothioate anti-sense oligonucleotides have been shown in the past to induce hypotension in some model systems. Furthermore, the adenosine A₁ receptor plays an important role in sinoatrial conduction within the heart. Attenuation of the adenosine A₁ receptor by anti-sense oligo I (SEQ. ID NO:1) might be expected to result, therefore, in deleterious extrapulmonary activity in response to the downregulation of the receptor. This is not the case. The anti-sense oligo I (SEQ. ID NO:1) does not produce any deleterious intrapulmonary effects and renders the administration of the low doses of the present anti-sense oligo free of unexpected, undesirable side effects.

This demonstrates that when oligo I (SEQ. ID NO:1) is administered directly to the lung, it does not reach the heart in significant quantities to cause deleterious effects. This is in contrast to traditional adenosine receptor antagonists like theophylline which do escape the lung and can cause deleterious, even life-threatening effects outside the lung.

#### Example 26: Long Lasting Effect of Oligo I

The Oligo I (SEQ. ID NO:1) evidenced a long lasting effect as evidenced by the PC50 and Resistance values obtained upon its administration prior to adenosine challenge.

The duration of the effect was measured for with respect to the  $PC_{50}$  of adenosine anti-sense oligo I when administered in four equal doses of 5 mg each by means of a nebulizer via an endotracheal tube, as described above. The effect of the agent is significant over days 1 to 8 after administration. When the effect of the anti-sense oligo I (SEQ. ID NO:1) had disappeared, the animals were administered saline aerosols (controls), and the  $PC_{50}$  Adenosine values for all animals were measured again. Saline-treated animals showed base line  $PC_{50}$  adenosine values (n=6).

The duration of the effect (with respect to Resistance) was measured for six allergic rabbits which were administered 20 mg of anti-sense oligo I (SEQ. ID NO: 1) as described above, upon airway

resistance measured as also described above. The mean calculated duration of effect was 8.3 days for both PC₅₀ adenosine (p<0.05) and resistance (p<0.05). These results show that anti-sense oligo I (SEQ. ID NO:1) has an extremely long duration of action, which is completely unexpected.

#### Example 27: Anti-sense Oligo II

Anti-sense oligo II, targeted to a different region of the adenosine  $A_1$  receptor mRNA, was found to be highly active against the adenosine  $A_1$ -mediated effects. The experiment measured the effect of the administration of anti-sense oligo II (SEQ. ID NO:997) upon compliance and resistance values when 20 mg anti-sense oligo II or saline (control) were administered to two groups of allergic rabbits as described above. Compliance and resistance values were measured following an administration of adenosine or saline as described above in Example 13. The effect of the anti-sense oligo of the invention was different from the control in a statistically significant manner, p<0.05 using paired t-test, compliance; p<0.01 for resistance.

The results showed that anti-sense oligo II (SEQ. ID NO:997), which targets the adenosine A₁ receptor, effectively maintains compliance and reduces resistance upon adenosine challenge.

### Example 28: Antisense Oligos III and IV

Oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) were shown to be in fact specifically targeted to the adenosine A₃ receptor by their effect on reducing inflammation and the number of inflammatory cells present upon separate administration of 20 mg of the anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) to allergic rabbits as described above. The number of inflammatory cells was determined in their bronchial lavage fluid 3 hours later by counting at least 100 viable cells per lavage.

The effect of anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) upon granulocytes, and upon total cells in bronchial lavage were assessed following exposure to dust mite allergen. The results showed that the anti-sense oligo IV (SEQ. ID NO:999) and anti-sense oligo III (SEQ. ID NO:998) are very potent anti-inflammatory agents in the asthmatic lung following exposure to dust mite allergen. As is known in the art, granulocytes, especially eosinophils, are the primary inflammatory cells of asthma, and the administration of anti-sense oligos III (SEQ. ID NO:998) and IV (SEQ. ID NO:999) reduced their numbers by 40% and 66%, respectively. Furthermore, anti-sense oligos IV (SEQ. ID NO:999) and III (SEQ. ID NO:998) also reduced the total number of cells in the bronchial lavage fluid by 40% and 80%, respectively. This is also an important indicator of anti-inflammatory activity by the present anti-adenosine A₃ agents of the invention. Inflammation is known to underlie bronchial hyperresponsiveness and allergen-induced bronchoconstriction in asthma. Both anti-sense oligonucleotides III (SEQ. ID NO:998) and IV (SEQ. ID NO:999), which are targeted to the adenosine A₃ receptor, are representative of an important new class of anti-inflammatory agents which may be designed to specifically target the lung receptors of each species.

## Example 29: Anti-sense Oligo V

The anti-sense oligo V (SEQ. ID NO:1000), targeted to the adenosine  $A_{2b}$  adenosine receptor mRNA was shown to be highly effective at countering adenosine  $A_{2b}$ -mediated effects and at reducing the number of adenosine  $A_{2b}$  receptors present to less than half.

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Example 30: Unexpected Superiority of Substituted over Phosphodiester-residue Oligo I-DS (SEQ. ID NO:1681)

Oligos I (SEQ. ID NO:1) and I-DS (SEQ. ID NO:1) were separately administered to allergic rabbits as described above, and the rabbits were then challenged with adenosine. The phosphodiester oligo I-DS (SEQ. ID NO:1) was statistically significantly less effective in countering the effect of adenosine whereas oligo I (SEQ. ID NO:1) showed high effectiveness, evidencing a PC50 Adenosine of 20 mg.

#### Example 31: Anti-sense Oligo VI

For the present work, I designed an additional anti-sense phosphorothioate oligo targeted to the adenosine A₁ receptor (Oligo VI). This anti-sense oligo was designed for therapy on a selected species as described in the above patent application and is generally specific for that species, unless the segment of the adenosine receptor mRNA of other species elected happens to have a similar sequence. The antisense oligos were prepared as described below, and tested in vivo in a rabbit model for bronchoconstriction, inflammation and lung allergy, which have breathing difficulties and impeded lung airways, as is the case in ailments such as asthma, as described in the above-identified application.

One additional oligo and its effect in a rabbit model was studied and the results of the study are reported and discussed below. The present oligo (anti-sense oligo VI) was selected for this study to complement the data on SEQ ID NO: 1 (Oligo I), which is anti-sense to the adenosine A₁ receptor mRNA provided in the above-identified patent application. This additional oligo is identified as anti-sense Oligo VI, and is targeted to a different region of the adenosine A₁ receptor mRNA than Oligo I. The design and synthesis of this anti-sense oligo was performed in accordance with the teaching, particularly Example 1, of the above-identified patent application.

The anti-sense Oligo VI is a phosphorothioate designed to target the coding region of the rabbit adenosine A₁ receptor mRNA region +964 to +984 relative to the initiation codon (start site). The Oligo VI was prepared as described in the above-indicated application, and is 20 nucleotides long. The OligoVI is directed to the adenosine A₁ receptor gene, and has the following sequence:

### 5'-CGC CGG CGG GTG CGG GCC GG-3' (SEQ. ID NO:1004)

The phosphorothioate anti-sense Oligo VI having the sequence described in (5) above, was synthesized on an Applied Biosystems Model 396 Oligonucleotide Synthesizer, and purified using NENSORB chromatography (DuPont, DE). TETD (tetraethylthiuram disulfide) was used as the sulfurizing agent during the synthesis.

#### **Example 32:** Preparation of Allergic Rabbits

Neonatal New Zealand white Pasturella-free rabbits were immunized intraperitoneally within 24 hours of birth with 0.5 ml of 312 antigen units/ml house dust mite (D. farinae) extract (Berkeley Biologicals, Berkeley, CA) mixed with 10% kaolin as previously described (Metzger, W. J., in Late Phase Allergic Reactions, Dorsch, W., Ed., CRC Handbook, pp 347-362, CRC Press, Boca Raton, 1990; Ali, S. Et al., Am. J. Resp. Crit. Care Med. 149: 908 (1994)).

The immunizations were repeated weekly for the first month and then bi-weekly until the animals were 4 months old. These rabbits preferentially produce allergen-specific IgE antibody, typically respond to aeroallergen challenge with both an early and late-phase asthmatic response, and show

bronchial hyper responsiveness (BHR). Monthly intraperitoneal administration of allergen (312 units dust mite allergen, as above) continues to stimulate and maintain allergen-specific IgE antibody and BHR. At 4 months of age, sensitized rabbits were prepared for aerosol administration as described by Ali et al. (1994), supra.

#### **Example 33:** Adenosine Aerosol Preparation

An adenosine aerosol (20 mg/ml) was prepared with an ultrasonic nebulizer (Model 646, DeVilbiss, Somerset, PA), which produced aerosol droplets, 80% of which were smaller than 5µm in diameter. Equal volumes of the aerosols were administered directly to the lungs via an intratracheal tube to all three rabbits.

The animals were then administered the aerosolized adenosine and Day 1 pre-treatment values for sensitivity to adenosine were calculated as the dose of adenosine causing a 50% loss of compliance (PC₅₀ Adenosine). The animals were then administered the aerosolized anti-sense via the intratracheal tube (5 mg/1.0 ml), for 2 minutes, twice daily for 2 days (total dose, 20 mg). Post-treatment PC₅₀ values were recorded (post-treatment challenge) on the morning of the third day. The results of these studies are provided in (9) below.

## **Example 34:** Anti-sense Oligo Formulation

Each one of anti-sense oligos were separately solubilized in an aqueous solution and administered as described for anti-sense oligo I in (e) above, in four 5 mg aliquots (20 mg total dose) by means of a nebulizer via endotracheal tube, as described above.

# Example 35: Oligo VI Reduces Response to Adenosine Challenge as Well or Better than Oligo I

Oligo VI was tested in three allergic rabbits of the characteristics and readied as described in (7) above and in the above-indicated patent application. Oligo VI targets a section of the coding region of the  $A_1$  receptor which is different from Oligo I. Both these target sequences were selected randomly from many possible coding region target sequences.

The three rabbits were treated identically as previously indicated for Oligo I. Briefly, 5 mg of Oligo VI were nebulized to the rabbits twice per day at 8 hour intervals, for two days. Thereafter, PC₅₀ adenosine studies were performed on the morning of the third day and compared to pre-treatment PC₅₀ values. This protocol is described in more detail in Nyce and Metzger (Nyce & Metzger, Nature 385: 721-725 (1997)). The results obtained for the three rabbits are shown in Table 5 below.

<u>Table 5</u>: PC₅₀ Adenosine before & after Aerosolized Adenosine Treatment

Treatment Time	PC ₅₀ Adenosine (mg)	
Pre-treatment	3.0 ±2.1	
Post-treatment	>20.0*	

^{*} maximum achievable dose due to adenosine insolubility in saline

All three animals treated with Oligo VI completely eliminated sensitivity to adenosine up to the measurable level of the agent shown in Table 1 above. That is, the administration of the Oligo VI abrogated the adenosine-induced bronchoconstriction in the three allergic rabbits. The actual efficacy of

Oligo VI is, therefore, greater than could be measured in the experimental system used.

By comparing with the previously submitted results for the Oligo I, it may be seen that the Oligo VI was found to be as effective, or more, than Oligo I.

# Example 36: Determination of Surfactant Depletion When A1 Receptors Are Expressed in Lung

This example shows the effect on the oligos of the invention on the level of lung phospholipid in an animal model for hypersensitivity to the adenosine  $A_1$  receptor. The leftmost column of Figure 4 shows the level of phospholipid present in the untreated allergic rabbit. When the adenosine  $A_1$  receptors in allergic rabbits were stimulated by aerosolized adenosine, there was a significant depletion of lung surfactant. See middle column in Figure 4. The administration of an an anti-sense oligonucleotide which has been shown to block adenosine  $A_1$  receptor expression (SEQ. ID NO:1). See, Nyce, JW and Metzger, WJ, Nature (1997). When oligo I (SEQ. ID NO:1) was administered to the allergic rabbit prior to the administration of adenosine, this adenosine- $A_1$  receptor-induced surfactant depletion was completely prevented. See rightmost column in Figure 4. This indicates that attenuation of the adenosine  $A_1$  receptor by administration of the present anti-sense oligonucleotides establishes normal surfactant secretion. This is applicable to the prevention of RDS by administration during gestation of the composition of the invention comprising either a down-regulating oligo for the  $A_1$  receptor or any agonist capable of stimulating the  $A_{2a}$  receptor. This would be very beneficial because currently available surfactant preparations used in the treatment of RDS are either incomplete or derived from animal sources.

#### Example 37: Effect of Oligo I on Inflammation

Rabbits were administered 5 mg Oligo I (SEQ. ID NO:I; EPI 2010) or saline (control) by nebulizer twice a day for two days and were then challenged with bacterial endotoxin administered by ear vein injection. Neutrophils, a key inflammatory cell in ARDS, were then quantitated (n= 3). The leftmost column represents a saline control (saline administered to the rabbit - same volume as treatment). The center column represents the high number of neutrophils elicited by treatment with endotoxin alone. The rightmost column shows a significant (statistically) decrease in the number of neutrophils produced upon treatment with the Oligo I. The data are shown in Figure 5. The results of the experimental test show a clear reduction in the number of neutrophils in the bronchial lavage fluid obtained from the Oligo I treated animals.

# Example 38: Effect of Oligo I on Edema

As in example 37, rabbits were administered 5 mg oligo I (SEQ. ID NO:I; EPI 2010) or saline (control) by nebulizer twice a day for two days and were then challenged with bacterial endotoxin administered by ear vein injection. The left-hand column represents the edema produced by bacterial endotoxin, and the right-hand column shows the prevention or alleviation of edema brought about by the oligo of the invention. Thus, the data show that oligo I (EPI 2010) reduced the lung edema caused by bacterial endotoxin.

### **Example 39:** Effect of Oligo I on Total Number of Inflammatory Cells

Rabbits were administered 5 mg oligo I (SEQ. ID NO:I; EPI 2010) or saline (control) by nebulizer twice a day for two days, and were then challenged with bacterial endotoxin administered by ear vein injection. The total number of cells, an indication of inflammation, was then quantitated in

bronchial lavage fluid obtained from each animal (n = 3). The results show a dramatic increase in the total number of cells upon challenge with bacterial endotoxin (middle bar) when compared to saline (leftmost bar). Finally, the administration of 5 mg of Oligo I shows a pronounced reduction in the total number of cells elicited by the endotoxin.

#### Example 40: Conclusions

The work described and results discussed in the examples clearly show that all anti-sense oligonucleotides designed in accordance with the teachings of this patent were found to be highly effective at countering or reducing effects mediated by the receptors they are targeted to. That is, each and all of the two anti-sense oligos targeting an adenosine  $A_1$  receptor mRNA, 1 anti-sense oligo targeting an adenosine  $A_{2b}$  receptor mRNA, and the 2 anti-sense oligos targeting an  $A_3$  receptor mRNA were shown capable of countering the effect of exogenously administered adenosine which is mediated by the specific receptor they are targeted to.

The activity of the anti-sense oligos of this invention, moreover, is specific to the target and substitutively fails to inhibit another target. In addition, the results presented also show that the administration of the present agents results in extremely low or non-existent deleterious side effects or toxicity.

This represents 100% success in providing agents that are highly effective and specific in the treatment of bronchoconstriction and/or inflammation. This invention is broadly applicable in the same manner to all gene(s) and corresponding mRNAs encoding proteins involved in or associated with airway diseases. A comparison of the phosphodiester and a version of the same oligonucleotide wherein the phosphodiester bonds are substituted with phosphorothioate bonds evidenced an unexpected superiority for the phosphothiorate oligonucleotide over the phosphodiester anti-sense oligo.

The foregoing examples are illustrative of the present invention, but are not to be construed as limiting thereof. The invention is furter defined by the following claims, with equivalents of the claims to be included therein.

#### Claims:

1. A pharmaceutical composition, comprising

an agent which, when administered to a subject is effective for preventing, alleviating and/or inhibiting adenosine-mediated cardiopulmonary and/or renal damage and/or failure, the agent being selected from the group consisting of

adenosine A2a receptor agonist agents,

nucleic acids which comprise one or more oligonucleotide (oligo) selected from the group consisting of oligos that are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of intron and exon borders selected from the group consisting of the 5' end, the 3' end and the juxta-section between coding and non-coding regions, and to all segments of mRNA(s) encoding an adenosine A1, A2a, A2b and A3 receptors having agonist activity at the an adenosine A1, A2b or A3 receptors or lacking agonist or having antagonist activity at the adenosine A2a receptor, which contain about 0 to less than about 15% adenosine (A), and

mixtures thereof; and

optionally one or more surfactants.

- 2. The composition of claim 1, wherein the oligo consists of up to about 10% A.
- 3. The composition of claim 2, wherein the oligo consists of up to about 5% A.
- 4. The composition of claim 3, wherein the oligo is A-free.
- 5. The composition of claim 4, further comprising an agent selected from the group consisting of diagnostic and therapeutic agents, preferably selected from the group consisting of adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating (agonist) agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, anti-allergic rhinitis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome (RDS and ARDS), pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, liver, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, imaging agents, cardiac stress testing agents, antibody therapy agents, phototherapeutic agents, adenosine, and other anti-arrhythmic agents.
- 6. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and flanking regions thereof of the adenosine A₁ receptor, which have agonistic activity, and of the adenosine A₂ receptor which have antagonistic or lack adenosine A₂ receptor activity, and optionally one or more surfactants.
- 7. The composition of claim 1, wherein the target gene is selected from the group consisting of genomic flanking regions, target genes, sequences comprising an initiation codon, sequences comprising 2 or more G and/or C nucleotides, mRNAs and flanking regions thereof of the adenosine A_{2b} and A₃ receptors having adenosine A_{2b} and A₃ receptor agonistic activity, and optionally one or more surfactants.

- 8. The composition of claim 1, wherein one or more adenosines (A) is(are) substituted by a universal base selected from the group consisting of heteroaromatic bases which bind to thymidine base but have antagonist or agonist activity of less than about 0.5 of the adenosine base agonist or antagonist activity at the adenosine A₁, A_{2a}, A_{2b} and A₃ receptors.
- 9. The composition of claim 1, wherein the agent is an adenosine A2a agonist agent, and the composition optionally comprises one or more surfactants.
- 10. The composition of claim 8, wherein the heteroaromatic bases are selected from the group consisting of pyrimidines and purines, which may be substituted by O, halo, NH₂, SH, SO, SO₂, SO₃, COOH and branched and fused primary and secondary amino, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, alkenoxy, acyl, cycloacyl, arylacyl, alkynoxy, cycloalkoxy, aroyl, arylthio, arylsulfoxyl, halocycloalkyl, alkylcycloalkyl, alkenylcycloalkyl, alkynylcycloalkyl, haloaryl, alkynylaryl, arylalkyl, arylalkenyl, arylalkynyl, arylcycloalkyl, which may be further substituted by O, halo, NH₂, primary, secondary and tertiary amine, SH, SO, SO₂, SO₃, cycloalkyl, heterocycloalkyl and heteroaryl.
- 11. The composition of claim 10, wherein the pyrimidines and purines are substituted at positions selected from the group consisting of positions 1, 2, 3, 4, 7 and 8.
- 12. The composition of claim 11, wherein the pyrimidines and purines are selected from the group consisting of theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylline, enprofylline and xantine having the chemical formula

wherein R¹ and R² are independently H, alkyl, alkenyl or alkynyl and R³ is H, aryl, dicycloalkyl, dicycloalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, O-cycloalkyl, O-cycloalkynyl, NH₂-alkylamino-ketoxyalkyloxy-aryl and mono and dialkylaminoalkyl-N-alkylamino-SO₂ aryl.

- 13. The composition of claim 12, wherein the universal base is selected from the group consisting of 3-nitropyrrole-2'-deoxynucleoside, 5-nitro-indole, 2-deoxyribosyl-(5-nitroindole), 2-deoxyribofuranosyl-(5-nitroindole), 2'-deoxyinosine, 2'-deoxynebularine, 6H, 8H-3,4-dihydropyrimido [4,5-c] oxazine-7-one or 2-amino-6-methoxyaminopurine.
- 14. The composition of claim 1, where one methylated cytosine (mC) is substituted for an unmethylated cytosine (C) if at least one CpG dinucleotide if present in the oligo(s).
- 15. The composition of claim 1, wherein at least one mononucleotide residue of the antisense oligonucleotide(s) is a residue selected from the group consisting of methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, methylene(methyimino), (MMI), methoxymethyl (MOM), methoxyethyl (MOE), methyleneoxy (methylimino) (MOMA), methoxy methyl (MOM), 2'-O-methyl, phosphoramidate, and C-5 substituted residues, and combinations thereof.

- 16. The composition of claim 1, wherein the anti-sense oligonucleotide comprises about 7 to about 60 mononucleotides.
- 17. The composition of claim 1, wherein the anti-sense oligonucleotide is selected from the group consisting of SEQ ID NOS.: 1, 3, 5, 7 and fragments 1-957 (SEQ. ID NO: 8-952) of SEQ. ID NO: 7 and SEQ. ID NOS: 953-999.
- 18. The composition of claim 1, wherein the anti-sense oligonucleotide is linked to an agent selected from the group consisting of cell internalized or up-taken agent(s) and cell targeting agents, which agent is preferably selected from the group consisting of transferrin, asialoglycoprotein and streptavidin.
  - 19. The composition of claim 18, wherein the nucleic acid is linked to a vector.
- 20. A vector, comprising the oligo of claim 19, wherein the vector is selected from the group consisting of prokaryotic or eukaryotic vectors.
  - 21. A cell, comprising the oligo of claim 1.
- 22. The composition of claim 1, further comprising a carrier, preferably a biologically acceptable carrier, and more preferably a pharmaceutically or veterinarily acceptable carrier.
- 23. The composition of claim 22, wherein the carrier is selected from the group consisting of gaseous, liquid, solid carriers and mixtures thereof.
- 24. The composition of claim 23, further comprising an agent selected from the group consisting of diagnostic and other therapeutic agents, antioxidants, flavoring and coloring agents, fillers, volatile oils, buffering agents, dispersants, surfactants, RNA inactivating agents, antioxidants, flavoring agents, propellants and preservatives.
- 25. The composition of claim 24, comprising the agent, a therapeutic agent, a surfactant and a pharmaceutically acceptable carrier.
- 26. The composition of claim 24, wherein the diagnostic and therapeutic agents are selected from the group consisting of other adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating agents, anti-inflammatory agents, contrast imaging agents, cardiac stress testing agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), ARDS, RDS, allergic rhinitis, hypoxia, cardiopulmonary and renal damage or failure, and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents and phototherapeutic agents.
- 27. The composition of claim 24, wherein the RNA inactivating agent comprises an enzyme, preferably a ribozyme.
- 28. The composition of claim 1, wherein the agent is present in an amount of about 0.01 to about 99.99 w/w of the composition, preferably about 1 to about 40 w/w of the composition.
- 29. A formulation, comprising the composition of claim 24, selected from the group consisting of systemic and topical formulations, preferably selected from the group consisting of oral, intrabuccal, intrapulmonary, rectal, intrauterine, intratumor, intracranial, nasal, intramuscular, subcutaneous, intravascular, intrathecal, inhalable, transdermal, intradermal, intracavitary, implantable,

iontophoretic, ocular, vaginal, intraarticular, otical, intravenous, intramuscular, intraglandular, intraorgan, intralymphatic, implantable, slow release and enteric coating formulations.

- 30. The formulation of claim 29, which is an oral formulation, wherein the carrier is selected from the group consisting of solid and liquid carriers.
- 31. The formulation of claim 30, wherein the liquid carrier is selected from the group consisting of solutions, suspensions, and oil-in-water and water-in-oil emulsions.
- 32. The formulation of claim 30, which is selected from the group consisting of a powder, dragees, tablets, capsules, sprays, aerosols, solutions, suspensions and emulsions.
- 33. The formulation of claim 29, which is a topical formulation, wherein the carrier is selected from the group consisting of creams, gels, ointments, sprays, aerosols, patches, solutions, suspensions and emulsions.
- 34. The formulation of claim 29, which is an injectable formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
  - 35. The formulation of claim 29, which is a rectal formulation in the form of a suppository.
- 36. The formulation of claim 29, which is a transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
- 37. The formulation of claim 36, which is an iontophoretic transdermal formulation, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions, and wherein the formulation further comprises a transdermal transport promoting agent.
  - 38. An implantable capsule or cartridge, comprising the formulation of claim 36.
- 39. The formulation of claim 29, wherein the carrier is selected from the group consisting of aqueous and alcoholic solutions and suspensions, oily solutions and suspensions and oil-in-water and water-in-oil emulsions.
- 40. The formulation of claim 29, wherein the carrier comprises a hydrophobic carrier, which is preferably lipid vesicles or particles, more preferably comprising liposomes or microcrystals.
- 41. The formulation of claim 40, wherein the vesicles comprise liposomes which comprise the agent.
- 42. The formulation of claim 40, wherein the vesicles comprise N-(1-[2, 3-dioleoxyloxi] propyl) -N,N,N- trimethyl- ammonium methylsulfate.
- 43. The formulation of claim 29, comprising a respirable or inhalable formulation, preferably an aerosol.
  - 44. The formulation of claim 29, in single or multiple unit form, or in bulk.
- 45. A kit for preventing or treating cardiac, lung and/or renal damage or failure, ARDS, RDS, comprising

a delivery device;

in a separate container, the formulation of claim 29; and

instructions for its use; and optionally, in a separate container, an agent selected from the group consisting of other therapeutic and diagnostic agents, surfactants, solvents, anti-oxidants, flavoring, fillers, volatile oils, dispersants, antioxidants, flavoring agents, propellants, preservatives and buffering,

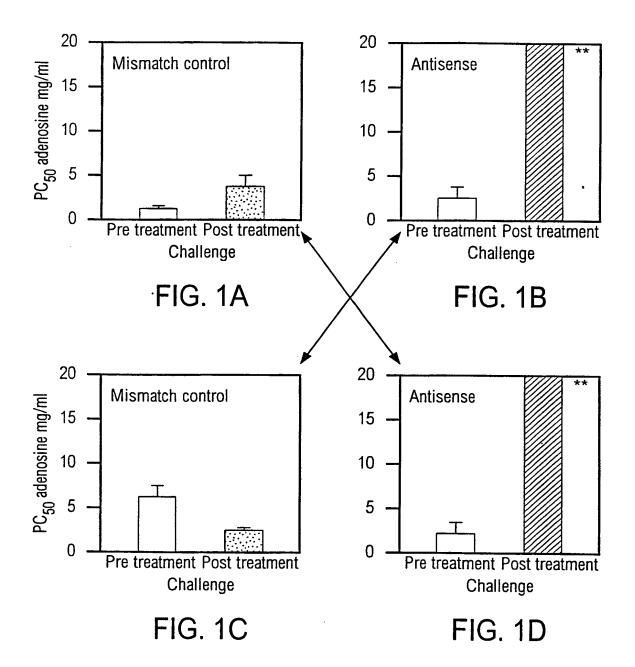
RNA inactivating, cell-internalized or up-taken and coloring agents...

- 46. The kit of claim 45, wherein the delivery device comprises a nebulizer which delivers single metered doses of the formulation.
- 47. The kit of claim 46, wherein the nebulizer comprises an insufflator; and the composition is provided in a piercable or openable capsule or cartridge.
- 48. The kit of claim 45, wherein the delivery device comprises a pressurized inhaler; and the composition comprises a suspension, solution or dry formulation of the agent and/or a solvent.
- 49. The kit of claim 45, comprising, in separate containers, a nucleic and therapeutic agents selected from the group consisting of other anti adenosine A₁, A_{2b} and A₃ receptor antagonists, adenosine A_{2a} receptor stimulants (agonists), anti-inflammatory agents, anti-bacterials, heart, lung and kidney activity maintenance and restoration agents, anti-cancer agents, adenosine, blood pressure controlling agents, and diuretics.
- 50. The kit of claim 45, wherein the solvent is selected from the group consisting of organic solvents and organic solvents mixed with one or more co-solvents.
  - 51. The kit of claim 45, wherein the composition is provided in a capsule or cartridge.
- 52. An in vivo method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to a subject suspected of being at risk for or being afflicted with, cardiac, lung and/or renal damage or failure, acute respiratory distress syndrome (ARDS), RDS, the composition of claim 1, comprising an amount of the agent effective for preventing or treating cardiac, lung and/or renal damage or failure, ARDS, RDS, anti-ARDS amount of the nucleic acid effective to reach and act on the target polynucleotide.
- 53. A method of preventing, alleviating or countering for preventing or treating adenosine receptor mediated cardiac, lung and/or renal damage or failure, acute respiratory distress syndrome (ARDS), RDS, allergic rhinitis and COPD, comprising conducting the method of claim 52.
- 54. The method of claim 52, wherein the composition is administered into the subject's respiratory system.
- 55. The method of claim 52, wherein the agent is an adenosine A2a agonist agent, the amount of agent administered is an anti-ARDS or anti-RDS associated bronchoconstriction effective amount, and the method is for preventing or treating ARDS.
- 56. The method of claim 52, wherein the agent is an adenosine A1 antagonist agent, the amount of agent administered is an anti-COPD associated bronchoconstriction effective amount, and the method is for preventing or treating COPD.
- 57. The method of claim 52, wherein the agent is an oligo anti-sense to the adenosine A3 receptor mRNA, the amount of agent administered is an anti-allergic rhinitis effective effective amount, and the method is for preventing or treating allergic rhinitis.
- 58. The method of claim 52, wherein the amount of agent administered is an antipulmonary, cardiac or renal hypoxic effective amount, and the method is for preventing or treating lung, heart and/or kidney damage and/or failure.
- 59. The method of claim 52, wherein the amount of agent administered is effective for preventing or treating cardiopulmonary hypoxia associated with the administration of stress test agents.
  - 60. The method of claim 52, wherein the amount of agent administered effective for

preventing or treating renal damage and/or failure associated with the administration od imaging agents.

- 61. The method of claim 52, wherein the agent is effective to reduce the production or availability or to increase the degradation of adenosine receptor mRNA or to reduce the amount of the adenosine receptor.
- 62. The method of claim 52, wherein the agent is administered directly into the subject's lung (s).
  - 63. The method of claim 52, wherein the agent is administered as a respirable aerosol.
- 64. The method of claim 52, wherein the disease or condition is associated with acute inflammation.
- 65. The method of claim 52, wherein the diagnostic or therapeutic agent is selected from the group consisting of adenosine A₁, A_{2b} and A₃ receptor inhibiting agents and adenosine A_{2a} receptor stimulating agents, anti-inflammatory agents, anti-bacterial agents, anti-sepsis agents, kidney activity maintenance and restoration agents and agents for the treatment of pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, respiratory distress syndrome, (RDS), acute respiratory distress syndrome (ARDS), allergic rhinitis, pain, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, chronic obstructive pulmonary disease (COPD), and cancers selected from the group consisting of leukemias, lymphomas and carcinomas of the colon, breast, lung, pancreas, hepatocellular carcinoma, kidney, melanoma, hepatic, lung, breast and prostate metastatic cancer, radiation agents, chemotherapeutic agents, antibody therapy agents, phototherapeutic agents, adenosine, and other anti-arrhythmic agents.
- 66. The method of claim 52, wherein the therapeutic agent is selected from the group consisting of anti-adenosine A₃ receptor agents.
  - 67. The method of claim 55, wherein ARDS is associated with sepsis.
- 68. The method of claim 52, wherein the composition is administered by a transdermal or systemic route.
- 69. The method of claim 68, wherein the composition is administered orally, intracavitarily, intranasally, intraanally, intravaginally, intrauterally, intraarticularly, transdermally, intrabucally, intravenously, subcutaneously, intradurally, intramuscularly, intravascularly, intratumorously, intraglandularly, intraocularly, intracranially, into an organ, intravascularly, intrathecally, intralymphatically, intraotically, intrathecally, by implantation, by inhalation, intradermally, intrapulmonarily, intraotically, by slow release, by sustained release and by a pump.
  - 70. The method of claim 52, wherein the subject is a mammal.
- 71. The method of claim 70, wherein the mammals are selected from the group consisting of humans and animals.
  - 72. The method of claim 71, wherein the mammal is a human.
  - 73. The method of claim 71, wherein the subject is an animal.
- 74. The method of claim 52, wherein the anti-sense oligonucleotide is administered in amount of about 0.005 to about 150 mg/kg body weight.
- 75. The method of claim 74, wherein the anti-sense oligonucleotide is administered in an amount of about 0.01 to about 75 mg/kg body weight.
- 76. The method of claim 75, wherein the anti-sense oligonucleotide is administered in an amount of about 1 to 50 mg/kg body weight.

- 77. The method of claim 52, which is a prophylactic or preventative method.
- 78. The method of claim 52, which is a therapeutic method.
- 79. The method of claim 52, wherein the oligo is obtained by
- (a) selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C;
- (b) obtaining a first oligonucleotide 4 to 60 nucleotide long which comprises the selected fragment and has a C and G nucleic acid content of about 0 to and including about 15%; and
- (c) obtaining a second oligonucleotide 4 to 60 nucleotide long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an A base content of up to and including about 15%.



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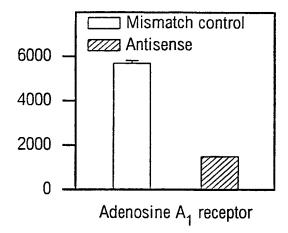


FIG. 2A

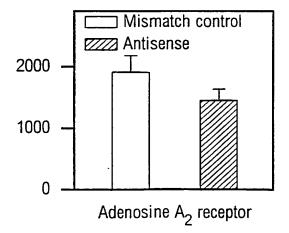


FIG. 2B

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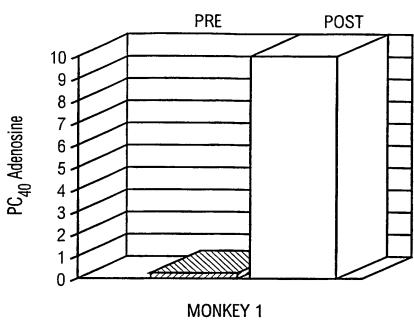


FIG. 3A

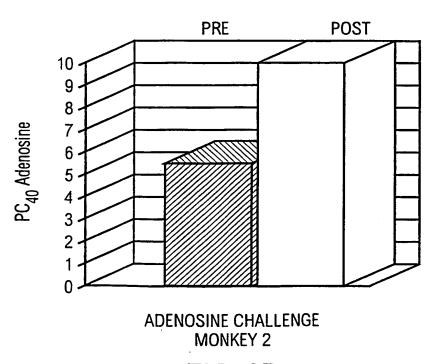


FIG. 3B

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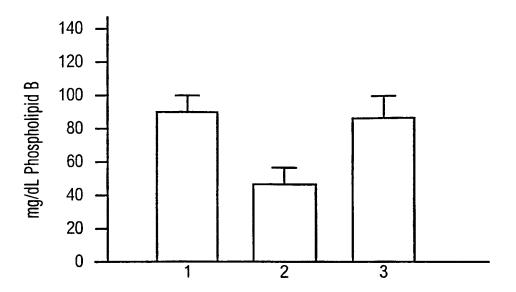


FIG. 4

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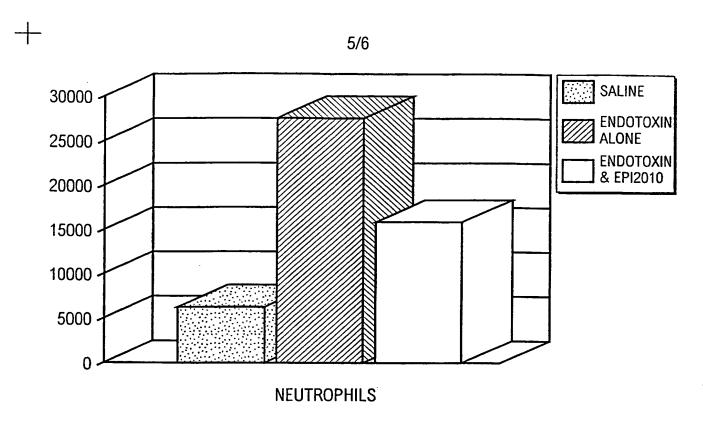
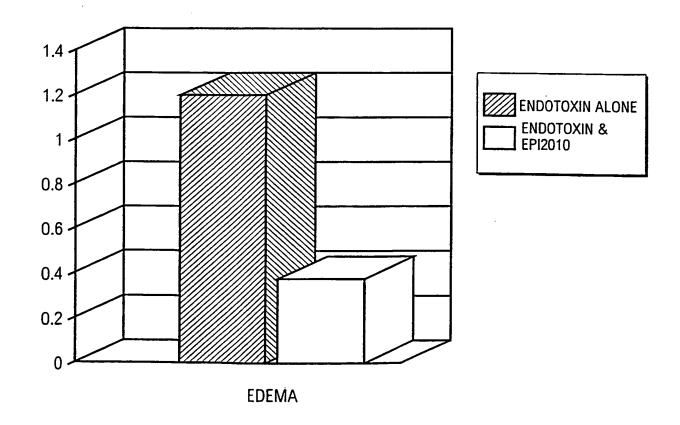


FIG. 5



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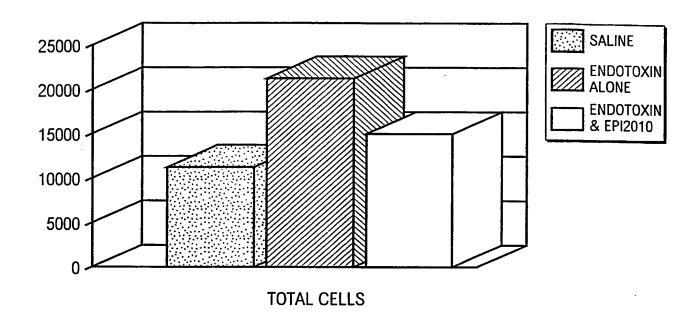


FIG. 7

SEQUENCE LISTING

```
(1) GENERAL INFORMATION:
      (i) APPLICANT: Nyce, Jonathan W. and Hill, Jeffrey
     (ii) TITLE OF INVENTION:
    (iii) NUMBER OF SEQUENCES: 1004
      (iv) CORRESPONDENCE ADDRESS:
           (A) ADDRESSEE: ARTER & HADDEN
           (B) STREET: 725 South Figueroa St.
           (C) CITY: Los Angeles
           (D) STATE: California
           (E) COUNTRY: USA
           (F) ZIP: 900071
     (v) COMPUTER READABLE FORM:
           (A) MEDIUM TYPE: Floppy disk
           (B) COMPUTER: IBM PC compatible
           (C) OPERATING SYSTEM: PC-DOS/MS-DOS
           (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
    (vi) CURRENT APPLICATION DATA:
          (A) APPLICATION NUMBER:
           (B) FILING DATE: 8-JUN-1999
          (C) CLASSIFICATION:
          (A) APPLICATION NUMBER: US 60/088,657
          (B) FILING DATE: 9-JUN-1998
          (C) CLASSIFICATION:
          (A) APPLICATION NUMBER: US 60/088,501
          (B) FILING DATE: 8-JUN-1998
          (C) CLASSIFICATION:
          (A) APPLICATION NUMBER: US 09/093,972
          (B) FILING DATE: 9-JUN-1998
           (C) CLASSIFICATION:
  (viii) ATTORNEY/AGENT INFORMATION:
           (A) NAME: Amzel, Viviana
           (B) REGISTRATION NUMBER: 30,930
           (C) REFERENCE/DOCKET NUMBER: EPI-179
    (ix) TELECOMMUNICATION INFORMATION:
           (A) TELEPHONE: 213-430-3520
          (B) TELEFAX: 213-617-9255
(C) TELEX:
(2) INFORMATION FOR SEQ ID NO:1:
     (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 21 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
GATGGAGGGC GGCATGGCGG G
                                                                           21
(2) INFORMATION FOR SEQ ID NO:2:
     (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 21 base pairs
          (B) TYPE: nucleic acid
          (C) STRANDEDNESS: single
          (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:
GTAGCAGGCG GGGATGGGGG C
                                                                           21
(2) INFORMATION FOR SEQ ID NO:3:
```

(i) SEQUENCE CHARACTERISTICS:

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(A) L; (B) T; (C) S; (D) T; (ii) MOLECU; (xi) SEQUEN;	CE CHARACTERISTICS: ENGTH: 42 base pairs YPE: nucleic acid TRANDEDNESS: single OPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:16: CTGAGA TGGAGGGCGG CATGGCGGCC AC	42
(i) SEQUENC (A) LI (B) TY (C) ST (D) TC (ii) MOLECUI (xi) SEQUENC	FOR SEQ ID NO:17: CE CHARACTERISTICS: ENGTH: 41 base pairs YPE: nucleic acid TRANDEDNESS: single OPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:17: CTGAGA TGGAGGGCGG CATGGCGGGC A	41
(i) SEQUENC (A) LE (B) TY (C) ST (D) TO (ii) MOLECUI (xi) SEQUENC	FOR SEQ ID NO:18: CE CHARACTERISTICS: ENGTH: 40 base pairs YPE: nucleic acid TRANDEDNESS: single OPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:18: CTGAGA TGGAGGGCGG CATGGCGGGC	40
(i) SEQUENC (A) LE (B) TY (C) ST (D) TC (ii) MOLECUI (xi) SEQUENC	FOR SEQ ID NO:19: CE CHARACTERISTICS: ENGTH: 39 base pairs YPE: nucleic acid TRANDEDNESS: single DPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:19: CTGAGA TGGAGGGCGG CATGGCGGG	39
(i) SEQUENC (A) LE (B) TY (C) ST (D) TO (ii) MOLECUI (xi) SEQUENC	FOR SEQ ID NO:20: CE CHARACTERISTICS: ENGTH: 38 base pairs YPE: nucleic acid TRANDEDNESS: single DPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:20: CTGAGA TGGAGGGCGG CATGGCGG	38
(i) SEQUENC (A) LE (B) TY (C) ST (D) TC (ii) MOLECUI (xi) SEQUENC	FOR SEQ ID NO:21: CE CHARACTERISTICS: ENGTH: 37 base pairs YPE: nucleic acid IRANDEDNESS: single DPOLOGY: linear LE TYPE: DNA (genomic) CE DESCRIPTION: SEQ ID NO:21: CTGAGA TGGAGGGCGG CATGGCG	27
(2) INFORMATION (i) SEQUENC (A) LE (B) TY	FOR SEQ ID NO:22: CE CHARACTERISTICS: ENGTH: 36 base pairs YPE: nucleic acid FRANDEDNESS: single	37

	INFORMATION FOR SEQ ID NO:29:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29: GGCCTGG AAAGCTGAGA TGGAGGGCG	29
	INFORMATION FOR SEQ ID NO:30:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30: GGCCTGG AAAGCTGAGA TGGAGGGC	28
	INFORMATION FOR SEQ ID NO:31:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:  GGCCTGG AAAGCTGAGA TGGAGGG	27
	INFORMATION FOR SEQ ID NO:32:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32: GCCCTGG AAAGCTGAGA TGGAGG	26
	INFORMATION FOR SEQ ID NO:33:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33: GCCTGG AAAGCTGAGA	25
	INFORMATION FOR SEQ ID NO:34:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: GCCTGG AAAGCTGAGA	24
(2)	INFORMATION FOR SEQ ID NO:35: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs	

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(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCCTGG AAAGCTGAGA TGG		23
(2) INFORMATION FOR SEQ ID NO:36:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGCGGCCTGG AAAGCTGAGA TG	NO:36:	22
(2) INFORMATION FOR SEQ ID NO:37:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCGGCCTGG AAAGCTGAGA T	NO:37:	21
(2) INFORMATION FOR SEQ ID NO:38:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGCGGCCTGG AAAGCTGAGA	NO:38:	20
(2) INFORMATION FOR SEQ ID NO:39:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCCTGG AAAGCTGAG	NO:39:	19
(2) INFORMATION FOR SEQ ID NO:40:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCCTGG AAAGCTGA	NO:40:	18
(2) INFORMATION FOR SEQ ID NO:41:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)		

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(ii) MOLECULE TYPE: DNA (genom: (xi) SEQUENCE DESCRIPTION: SEQ GCGGCCTGGA AAGCTGAGAT GGAGGG	ic)	26
(2) INFORMATION FOR SEQ ID NO:74:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi  (xi) SEQUENCE DESCRIPTION: SEQ  GCGGCCTGGA AAGCTGAGAT GGAGG	ic)	25
(2) INFORMATION FOR SEQ ID NO:75:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (**i) SEQUENCE DESCRIPTION: SEQ	.c)	
GCGGCCTGGA AAGCTGAGAT GGAG		24
(2) INFORMATION FOR SEQ ID NO:76:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ GCGGCCTGGA AAGCTGAGAT GGA	c)	23
(2) INFORMATION FOR SEQ ID NO:77:		
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQUENCE	c)	22
(2) INFORMATION FOR SEQ ID NO:78:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I	E) ID NO:78:	
		21
(2) INFORMATION FOR SEQ ID NO:79:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic	· =)	
(xi) SEQUENCE DESCRIPTION: SEQ I	ID NO:79:	

(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:  GCGGCCTGGA AAG	13
(2) INFORMATION FOR SEQ ID NO:87:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 12 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87: GCGGCCTGGA AA	12
(2) INFORMATION FOR SEQ ID NO:88:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:  GCGGCCTGGA A	11
(2) INFORMATION FOR SEQ ID NO:89:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 10 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89: GCGGCCTGGA	10
(2) INFORMATION FOR SEQ ID NO:90:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 49 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<ul><li>(ii) MOLECULE TYPE: DNA (genomic)</li><li>(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:</li><li>CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC</li></ul>	49
(2) INFORMATION FOR SEQ ID NO:91:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 48 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCCGGGCAC AGGCTGGG	48
(2) INFORMATION FOR SEQ ID NO:92:    (i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 47 base pairs	

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	INFORMATION FOR SEQ ID NO:118:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118: GCCTGGAA AGCTGAGATG G	21
(2)	INFORMATION FOR SEQ ID NO:119:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:  GCCTGGAA AGCTGAGATG	20
	INFORMATION FOR SEQ ID NO:120:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:  GCCTGGAA AGCTGAGAT	19
	INFORMATION FOR SEQ ID NO:121:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:  GCCTGGAA AGCTGAGA	18
	INFORMATION FOR SEQ ID NO:122:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:  CCCTGGAA AGCTGAG	17
	INFORMATION FOR SEQ ID NO:123:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:  CCCTGGAA AGCTGA	16
(2)	INFORMATION FOR SEQ ID NO:124: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 15 base pairs	

GGCCTGGAAA GCTGAGATGG AGG

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:155:

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(xi) SEQUENCE DESCRIPT GGCCTGGAAA GCTGAG		16
(2) INFORMATION FOR SEQ ID  (i) SEQUENCE CHARACTER  (A) LENGTH: 15 be  (B) TYPE: nucleid  (C) STRANDEDNESS:  (D) TOPOLOGY: lin  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTE  GGCCTGGAAA GCTGA	RISTICS: ase pairs c acid : single near A (genomic)	15
(2) INFORMATION FOR SEQ ID  (i) SEQUENCE CHARACTEF  (A) LENGTH: 14 ba  (B) TYPE: nucleid  (C) STRANDEDNESS:  (D) TOPOLOGY: lin  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTI	RISTICS: ase pairs c acid c single near A (genomic)	
GGCCTGGAAA GCTG	.on. 552 15 NO.104.	14
(2) INFORMATION FOR SEQ ID  (i) SEQUENCE CHARACTER  (A) LENGTH: 13 ba  (B) TYPE: nucleic  (C) STRANDEDNESS:  (D) TOPOLOGY: lin  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTI	RISTICS: use pairs cacid single uear u (genomic)	
GGCCTGGAAA GCT		13
(2) INFORMATION FOR SEQ ID  (i) SEQUENCE CHARACTER  (A) LENGTH: 12 ba  (B) TYPE: nucleic  (C) STRANDEDNESS:  (D) TOPOLOGY: lin  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTI  GGCCTGGAAA GC	ISTICS: se pairs acid single ear (genomic)	12
(2) INFORMATION FOR SEQ ID  (i) SEQUENCE CHARACTER  (A) LENGTH: 11 ba  (B) TYPE: nucleic  (C) STRANDEDNESS:  (D) TOPOLOGY: line  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTION  GGCCTGGAAA G	ISTICS: se pairs acid single ear (genomic)	11
(2) INFORMATION FOR SEQ ID (i) SEQUENCE CHARACTER:  (A) LENGTH: 10 bas  (B) TYPE: nucleic  (C) STRANDEDNESS:  (D) TOPOLOGY: line  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTION	ISTICS: se pairs acid single ear (genomic)	
GGCCTGGAAA		10
(2) INFORMATION FOR SEQ ID 1	NO:169:	

	INFORMATION FOR SEQ ID NO:182:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:  GGAAAG CTGAGATGGA GGGCGGCATG GCGG	34
	INFORMATION FOR SEQ ID NO:183:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:183: GGAAAG CTGAGATGGA GGGCGGCATG GCG	33
	INFORMATION FOR SEQ ID NO:184:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:  GGAAAG CTGAGATGGA GGGCGGCATG GC	32
	INFORMATION FOR SEQ ID NO:185:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:185: GGAAAG CTGAGATGGA GGGCGGCATG G	31
	INFORMATION FOR SEQ ID NO:186:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:186: GGAAAG CTGAGATGGA GGGCGGCATG	30
,	INFORMATION FOR SEQ ID NO:187:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:187:  GGAAAG CTGAGATGGA GGGCGGCAT	29
(2) ]	INFORMATION FOR SEQ ID NO:188: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	

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32 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:194: GCCTGGAAAG CTGAGATGGA GG	
(2) INFORMATION FOR SEQ ID NO:195:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:195: GCCTGGAAAG CTGAGATGGA G	22
(2) INFORMATION FOR SEQ ID NO:196:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:196: GCCTGGAAAG CTGAGATGGA	20
(2) INFORMATION FOR SEQ ID NO:197:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:197:  GCCTGGAAAG CTGAGATGG	19
(2) INFORMATION FOR SEQ ID NO:198:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:198: GCCTGGAAAG CTGAGATG	18
(2) INFORMATION FOR SEQ ID NO:199:     (i) SEQUENCE CHARACTERISTICS:      (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:199: GCCTGGAAAG CTGAGAT	17
(2) INFORMATION FOR SEQ ID NO:200:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:200:  GCCTGGAAAG CTGAGA	16
(2) INFORMATION FOR SEQ ID NO:201:	

(2) INFORMATION FOR SEQ ID NO:214:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:214: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAG	39
(2) INFORMATION FOR SEQ ID NO:215:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:215: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACA	38
(2) INFORMATION FOR SEQ ID NO:216:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 37 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:216: CCTGGAAAGC TGAGATGGAG GGCGCATGG CGGGCAC	37
(2) INFORMATION FOR SEQ ID NO:217:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 36 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:217: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCA	36
(2) INFORMATION FOR SEQ ID NO:218:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 35 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:218: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGCC	25
(2) INFORMATION FOR SEQ ID NO:219:	35
<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 34 base pairs</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> <li>(ii) MOLECULE TYPE: DNA (genomic)</li> <li>(xi) SEQUENCE DESCRIPTION: SEO ID NO.219.</li> </ul>	
CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGG	34
(2) INFORMATION FOR SEQ ID NO:220:	

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(xi) SEQUENCE DESCRIPTION: SE CCTGGAAAGC TGAGATGGAG G		. 21
(2) INFORMATION FOR SEQ ID NO:233 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 20 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomical sequences) (xi) SEQUENCE DESCRIPTION: SEC	: rs e mic)	20
(2) INFORMATION FOR SEQ ID NO:234  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 19 base pai:  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genor (xi) SEQUENCE DESCRIPTION: SEC	: rs e nic)	19
(2) INFORMATION FOR SEQ ID NO:235:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome acid) SEQUENCE DESCRIPTION: SEQUENCE OF SECUENCE	e e nic)	18
(2) INFORMATION FOR SEQ ID NO:236:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEC	rs :	17
(2) INFORMATION FOR SEQ ID NO:237:		
(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQUENCE OF COTTION (COTTION)	ic)	16
(2) INFORMATION FOR SEQ ID NO:238:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQ  CCTGGAAAGC TGAGA	s ic)	15

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(B) TYPE: nucleic (C) STRANDEDNESS: (D) TOPOLOGY: line (ii) MOLECULE TYPE: DNA (xi) SEQUENCE DESCRIPTIO CTGGAAAGCT GAGATGGAGG GCGGCA	single ar (genomic) N: SEO ID NO:245:	44
(2) INFORMATION FOR SEQ ID N (i) SEQUENCE CHARACTERI (A) LENGTH: 43 bas (B) TYPE: nucleic (C) STRANDEDNESS: (D) TOPOLOGY: line (ii) MOLECULE TYPE: DNA	STICS: e pairs acid single ar (genomic)	
(xi) SEQUENCE DESCRIPTION CTGGAAAGCT GAGATGGAGG GCGGCA  (2) INFORMATION FOR SEQ ID NO	TGGC GGGCACAGGC TGG O:247:	43
(i) SEQUENCE CHARACTERIS  (A) LENGTH: 42 base  (B) TYPE: nucleic a  (C) STRANDEDNESS: 3  (D) TOPOLOGY: linea  (ii) MOLECULE TYPE: DNA  (xi) SEQUENCE DESCRIPTION  CTGGAAAGCT GAGATGGAGG GCGGCA	STICS: e pairs acid single ar (genomic) N: SEO ID NO:247:	42
(2) INFORMATION FOR SEQ ID NO    (i) SEQUENCE CHARACTERIS    (A) LENGTH: 41 base    (B) TYPE: nucleic a    (C) STRANDEDNESS: (D) TOPOLOGY: linea    (ii) MOLECULE TYPE: DNA    (xi) SEQUENCE DESCRIPTION CTGGAAAGCT GAGATGGAGG GCGGCAT	STICS: e pairs acid single ar (genomic) N: SEO ID NO:248:	41
(2) INFORMATION FOR SEQ ID NO  (i) SEQUENCE CHARACTERIS  (A) LENGTH: 40 base  (B) TYPE: nucleic a  (C) STRANDEDNESS: S  (D) TOPOLOGY: linea  (ii) MOLECULE TYPE: DNA (  (xi) SEQUENCE DESCRIPTION  CTGGAAAGCT GAGATGGAGG GCGGCAT	STICS:  pairs  acid  single  ar  (genomic)  N: SEO ID NO:249:	40
(2) INFORMATION FOR SEQ ID NO    (i) SEQUENCE CHARACTERIS    (A) LENGTH: 39 base    (B) TYPE: nucleic a    (C) STRANDEDNESS: s    (D) TOPOLOGY: linea    (ii) MOLECULE TYPE: DNA (    (xi) SEQUENCE DESCRIPTION    CTGGAAAGCT GAGATGGAGG GCGGCAT	STICS: e pairs acid single ar (genomic) N: SEO ID NO:250:	
(2) INFORMATION FOR SEQ ID NO   (i) SEQUENCE CHARACTERIS   (A) LENGTH: 38 base   (B) TYPE: nucleic a   (C) STRANDEDNESS: s   (D) TOPOLOGY: linea   (ii) MOLECULE TYPE: DNA (	0:251: STICS: e pairs acid single	39

	INFORMATION FOR SEQ ID NO:271:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:271: GAAAGCT GAGATGGA	18
	<pre>INFORMATION FOR SEQ ID NO:272:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:272: GAAAGCT GAGATGG</pre>	17
	INFORMATION FOR SEQ ID NO:273:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:273:  GAAAGCT GAGATG	16
	INFORMATION FOR SEQ ID NO:274:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:274: GAAAGCT GAGAT	15
-	INFORMATION FOR SEQ ID NO:275:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:275: GAAAGCT GAGA	14
	INFORMATION FOR SEQ ID NO:276:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:276:  AAAGCT GAG	13
(2)	INFORMATION FOR SEQ ID NO:277:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs	

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ 1 TGGAAAGCTG AGATGGAGGG CGGCATGG	c)	28
(2) INFORMATION FOR SEQ ID NO:297:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I	c) ID NO:297:	27
(2) INFORMATION FOR SEQ ID NO:298:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I	:) ID NO:298:	26
(2) INFORMATION FOR SEQ ID NO:299:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 25 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I TGGAAAGCTG AGATGGAGGG CGGCA	:) :D NO:299:	25
(2) INFORMATION FOR SEQ ID NO:300:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic  (xi) SEQUENCE DESCRIPTION: SEQ INTEGGAAAGCTG AGATGGAGGG CGGC	:) ID NO:300:	24
(2) INFORMATION FOR SEQ ID NO:301:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ INTEGGAAAGCTG AGATGGAGGG CGG	) D NO:301:	23
(2) INFORMATION FOR SEQ ID NO:302:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ INTEGGAAAGCTG AGATGGAGGG CG	) D NO:302:	22

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16

(2) INFORMATION FOR SEQ ID NO:303:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:303: TGGAAAGCTG AGATGGAGGG C

TON FOR SEC ID NO. 204.

(2) INFORMATION FOR SEQ ID NO:304:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:304:

TGGAAAGCTG AGATGGAGGG 20

(2) INFORMATION FOR SEQ ID NO:305:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:305:
TGGAAAGCTG AGATGGAGG

(2) INFORMATION FOR SEQ ID NO:306:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 18 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:306:

(X1) SEQUENCE DESCRIPTION: SEQ ID NO:306:
TGGAAAGCTG AGATGGAG
18

(2) INFORMATION FOR SEQ ID NO:307:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 17 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:307:

TGGAAAGCTG AGATGGA 17

(2) INFORMATION FOR SEQ ID NO:308:
 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 16 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:308:
TGGAAAGCTG AGATGG

(2) INFORMATION FOR SEQ ID NO:309:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 15 base pairs

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(B) TYPE: nucl	50	
(C) STRANDEDNE (D) TOPOLOGY: (ii) MOLECULE TYPE:	ESS: single linear	
(2) INFORMATION FOR SEQ (i) SEQUENCE CHARAC (A) LENGTH: 14 (B) TYPE: nucl (C) STRANDEDNE (D) TOPOLOGY: (ii) MOLECULE TYPE:	CTERISTICS:   base pairs  eic acid  CSS: single  linear	
(xi) SEQUENCE DESCRI TGGAAAGCTG AGAT	PTION: SEQ ID NO:310:	14
(2) INFORMATION FOR SEQ (i) SEQUENCE CHARAC (A) LENGTH: 13 (B) TYPE: nucl (C) STRANDEDNE (D) TOPOLOGY:	TERISTICS: base pairs eic acid SS: single	
(ii) MOLECULE TYPE:	DNA (genomic) PTION: SEQ ID NO:311:	13
(0) 7,770		13
(2) INFORMATION FOR SEQ (i) SEQUENCE CHARAC (A) LENGTH: 12 (B) TYPE: nucl (C) STRANDEDNE (D) TOPOLOGY: (ii) MOLECULE TYPE:	TERISTICS: base pairs eic acid SS: single linear DNA (genomic)	
TGGAAAGCTG AG	PTION: SEQ ID NO:312:	12
(2) INFORMATION FOR SEQ (i) SEQUENCE CHARACY (A) LENGTH: 11 (B) TYPE: nucl (C) STRANDEDNE: (D) TOPOLOGY: (ii) MOLECULE TYPE: 1 (xi) SEQUENCE DESCRIPTION	TERISTICS: base pairs eic acid SS: single linear	12
IGGAAAGCIG A		11
(2) INFORMATION FOR SEQ :  (i) SEQUENCE CHARACT  (A) LENGTH: 10  (B) TYPE: nucle  (C) STRANDEDNES  (D) TOPOLOGY: 1  (ii) MOLECULE TYPE: I	TERISTICS: base pairs eic acid SS: single linear	
TGGAAAGCTG		10
(2) INFORMATION FOR SEQ I (i) SEQUENCE CHARACT  (A) LENGTH: 43  (B) TYPE: nucle  (C) STRANDEDNES  (D) TOPOLOGY: 1	TERISTICS: base pairs eic acid SS: single linear	
(ii) MOLECULE TYPE: [	ONA (genomic)	

(i) SEQ (A (B (C (D (ii) MOL (xi) SEQ	ION FOR SEQ ID NO:335: UENCE CHARACTERISTICS: ) LENGTH: 23 base pairs ) TYPE: nucleic acid ) STRANDEDNESS: single ) TOPOLOGY: linear ECULE TYPE: DNA (genomic) UENCE DESCRIPTION: SEQ ID ATGGAGGGC GGC		:3
(i) SEQ (A (B (C (D (ii) MOL)	ION FOR SEQ ID NO:336: UENCE CHARACTERISTICS: ) LENGTH: 22 base pairs ) TYPE: nucleic acid ) STRANDEDNESS: single ) TOPOLOGY: linear ECULE TYPE: DNA (genomic) UENCE DESCRIPTION: SEQ ID ATGGAGGGC GG		2
(i) SEQU (A) (B) (C) (D) (ii) MOLH	ION FOR SEQ ID NO:337:  JENCE CHARACTERISTICS:  LENGTH: 21 base pairs  TYPE: nucleic acid  STRANDEDNESS: single  TOPOLOGY: linear  ECULE TYPE: DNA (genomic)  JENCE DESCRIPTION: SEQ ID  ATGGAGGGC G		1
(i) SEQU (A) (B) (C) (D) (ii) MOLE	JON FOR SEQ ID NO:338: JENCE CHARACTERISTICS: LENGTH: 20 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CCULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID	NO:338:	0
(i) SEQUENCE (A) (B) (C) (D) (ii) MOLE	CON FOR SEQ ID NO:339: CHARACTERISTICS: LENGTH: 19 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CCULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID	NO:339:	9
(i) SEQU (A) (B) (C) (D) (ii) MOLE	CON FOR SEQ ID NO:340: DENCE CHARACTERISTICS: LENGTH: 18 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CCULE TYPE: DNA (genomic) DENCE DESCRIPTION: SEQ ID TTGGAGG	NO:340:	8
(i) SEQU	ON FOR SEQ ID NO:341: ENCE CHARACTERISTICS: LENGTH: 17 base pairs		

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(xi) SEQUENCE DESCRIPTION: SI	<del>-</del> -	
GGAAAGCTGA G	- 2 10 10 10 17 1	11
(2) INFORMATION FOR SEQ ID NO:348  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 10 base paid  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singly  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome)  (xi) SEQUENCE DESCRIPTION: SEGGAAAGCTGA	S: irs le omic)	10
(2) INFORMATION FOR SEQ ID NO:349  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 42 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (gence)  (xi) SEQUENCE DESCRIPTION: SEGAAAGCTGAG ATGGAGGGCG GCATGGCGGG	S: rs .e omic) GQ ID NO:349:	42
(2) INFORMATION FOR SEQ ID NO:350  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 41 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (geno  (xi) SEQUENCE DESCRIPTION: SE  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG	: rs e mic) O ID NO:350:	41
(2) INFORMATION FOR SEQ ID NO:351  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 40 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (geno  (xi) SEQUENCE DESCRIPTION: SE  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG	: rs e mic) O ID NO:351:	40
(2) INFORMATION FOR SEQ ID NO:352  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 39 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomer)  (xi) SEQUENCE DESCRIPTION: SE  GAAAGCTGAG ATGGAGGGCG GCATGGCGGG	: rs e mic) O ID NO:352:	39
(2) INFORMATION FOR SEQ ID NO:353 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 38 base pai. (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome in the second in the se	: rs e mic) Q ID NO:353: CACAGGCT	38
(2) INFORMATION FOR SEQ ID NO:354	:	

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (gend (xi) SEQUENCE DESCRIPTION: SEGAAAGCTGAG ATGGAGGGCG GCATGGCGGG	omic) EQ ID NO:360:	31
(2) INFORMATION FOR SEQ ID NO:36:  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 30 base pass  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomy)  (xi) SEQUENCE DESCRIPTION: SEGAAAGCTGAG ATGGAGGGCG GCATGGCGGG	S: irs le omic)	30
(2) INFORMATION FOR SEQ ID NO:362 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 29 base pair (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome) (xi) SEQUENCE DESCRIPTION: SEGAAAGCTGAG ATGGAGGGCG GCATGGCGG	S: irs le omic)	29
(2) INFORMATION FOR SEQ ID NO:363  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 28 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (geno  (xi) SEQUENCE DESCRIPTION: SE  GAAAGCTGAG ATGGAGGGCG GCATGGCG	S: .rs .e omic)	28
(2) INFORMATION FOR SEQ ID NO:364 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 27 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (geno (xi) SEQUENCE DESCRIPTION: SE GAAAGCTGAG ATGGAGGGCG GCATGGC	e mic)	27
(2) INFORMATION FOR SEQ ID NO:365 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 26 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome) (xi) SEQUENCE DESCRIPTION: SEGAAAGCTGAG ATGGAGGGCG GCATGG	: rs e mic)	26
(2) INFORMATION FOR SEQ ID NO:366 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 25 base paid (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome (xi) SEQUENCE DESCRIPTION: SEG	: rs e mic)	25

(2) INFORMATION FOR SEQ ID NO:367:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 24 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:367: GAAAGCTGAG ATGGAGGGCG GCAT	24
(2) INFORMATION FOR SEQ ID NO:368:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 23 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:368: GAAAGCTGAG ATGGAGGGCG GCA	23
(2) INFORMATION FOR SEQ ID NO:369:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 22 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:369: GAAAGCTGAG ATGGAGGGCG GC	22
(2) INFORMATION FOR SEQ ID NO:370:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:370: GAAAGCTGAG ATGGAGGGCG G	21
(2) INFORMATION FOR SEQ ID NO:371:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:371: GAAAGCTGAG ATGGAGGGCG	20
(2) INFORMATION FOR SEQ ID NO:372:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:372:  GAAAGCTGAG ATGGAGGGC	19
(2) INFORMATION FOR SEQ ID NO:373: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs	-

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:379: GAAAGCTGAG AT	12
(2) INFORMATION FOR SEQ ID NO:380:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:380:  GAAAGCTGAG A	11
(2) INFORMATION FOR SEQ ID NO:381:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:381:  GAAAGCTGAG	10
(2) INFORMATION FOR SEQ ID NO:382:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 41 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:382:  AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C	41
(2) INFORMATION FOR SEQ ID NO:383:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 40 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:383:  AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG	40
(2) INFORMATION FOR SEQ ID NO:384:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 39 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:384:  AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGG	39
(2) INFORMATION FOR SEQ ID NO:385:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:385:  AAAGCTGAGA TGGAGGGCGG CATGGCGGCC ACAGGCTG	38
(2) INFORMATION FOR SEQ ID NO:386:	

(	INFORMATION FOR SEQ ID NO:399:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGA TGGAGGGCGG CATG	NO:399:	24
(	INFORMATION FOR SEQ ID NO:400:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGA TGGAGGGCGG CAT	NO:400:	23
(	INFORMATION FOR SEQ ID NO:401:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGA TGGAGGGCGG CA	NO:401:	22
(	INFORMATION FOR SEQ ID NO:402:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID  TGAGA TGGAGGGCGG C	NO:402:	21
(	NFORMATION FOR SEQ ID NO:403:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID TGAGA TGGAGGGCGG	NO:403:	20
(. (:	NFORMATION FOR SEQ ID NO:404:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  ii) MOLECULE TYPE: DNA (genomic)  xi) SEQUENCE DESCRIPTION: SEQ ID  TGAGA TGGAGGGCG	NO:404:	19
(2) I	NFORMATION FOR SEQ ID NO:405: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs		

	INFORMATION FOR SEQ ID NO:431:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGAT GGAGGGCGGC ATG	NO:431:	23
	INFORMATION FOR SEQ ID NO:432:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGAT GGAGGGCGGC AT	NO: 432:	22
	INFORMATION FOR SEQ ID NO:433:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CTGAGAT GGAGGGCGGC A	NO:433:	21
	INFORMATION FOR SEQ ID NO:434:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID ECTGAGAT GGAGGGCGGC	NO:434:	20
	INFORMATION FOR SEQ ID NO:435:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID 19 CTGAGAT GGAGGGCGG	NO:435:	19
	INFORMATION FOR SEQ ID NO:436:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID 19  TGAGGAT GGAGGGCG	NO:436:	18
(2)	<pre>INFORMATION FOR SEQ ID NO:437:   (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 17 base pairs</pre>		

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(A (B (C (D (ii) MOL) (xi) SEQ	UENCE CHARACTERISTICS:  ) LENGTH: 34 base pairs  ) TYPE: nucleic acid  ) STRANDEDNESS: single  ) TOPOLOGY: linear  ECULE TYPE: DNA (genomic)  JENCE DESCRIPTION: SEQ ID  AGGGCGGCAC AGGC	NO:450:	. 34
(i) SEQU (A) (B) (C) (D) (ii) MOLH (xi) SEQU	ION FOR SEQ ID NO:451: JENCE CHARACTERISTICS: LENGTH: 33 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CCULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID AGGGCCGCA TGGCGGGCAC AGG	NO:451:	33
(i) SEQU (A) (B) (C) (D) (ii) MOLE (xi) SEQU	JON FOR SEQ ID NO:452: JENCE CHARACTERISTICS: LENGTH: 32 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CCULE TYPE: DNA (genomic) JENCE DESCRIPTION: SEQ ID LOGGGCGGCA TGGCGGGCAC AG	NO:452:	32
(i) SEQU (A) (B) (C) (D) (ii) MOLE (xi) SEQU	ON FOR SEQ ID NO:453: ENCE CHARACTERISTICS: LENGTH: 31 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CULE TYPE: DNA (genomic) ENCE DESCRIPTION: SEQ ID GGGCGGCA TGGCGGGCAC A	NO:453:	31
(i) SEQU (A) (B) (C) (D) (ii) MOLE (xi) SEQU	ON FOR SEQ ID NO:454: ENCE CHARACTERISTICS: LENGTH: 30 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CULE TYPE: DNA (genomic) ENCE DESCRIPTION: SEQ ID GGGCGGCA TGGCGGGCAC	NO:454:	. 30
(i) SEQU (A) (B) (C) (D) (ii) MOLE (xi) SEQU	ON FOR SEQ ID NO:455: ENCE CHARACTERISTICS: LENGTH: 29 base pairs TYPE: nucleic acid STRANDEDNESS: single TOPOLOGY: linear CULE TYPE: DNA (genomic) ENCE DESCRIPTION: SEQ ID GGGCGGCA TGGCGGGCA	NO:455:	29
(i) SEQU (A) (B)	ON FOR SEQ ID NO:456: ENCE CHARACTERISTICS: LENGTH: 28 base pairs TYPE: nucleic acid STRANDEDNESS: single		

(2) INFORMATION FOR SEQ ID NO:463: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:463: AGCTGAGATG GAGGGCGGCA T 21 (2) INFORMATION FOR SEQ ID NO: 464: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 20 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:464: AGCTGAGATG GAGGGCGGCA 20 (2) INFORMATION FOR SEQ ID NO: 465: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 19 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:465: AGCTGAGATG GAGGGCGGC 19 (2) INFORMATION FOR SEQ ID NO:466: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 466: AGCTGAGATG GAGGGCGG 18 (2) INFORMATION FOR SEQ ID NO: 467: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 17 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 467: AGCTGAGATG GAGGGCG 17 (2) INFORMATION FOR SEQ ID NO:468: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 16 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:468: AGCTGAGATG GAGGGC 16 (2) INFORMATION FOR SEQ ID NO:469: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(2) INFORMATION FOR SEQ ID NO:495:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	·
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:495: GCTGAGATGG AGGGCGGC	18
(2) INFORMATION FOR SEQ ID NO:496:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:496: GCTGAGATGG AGGGCGG	17
(2) INFORMATION FOR SEQ ID NO:497:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:497: GCTGAGATGG AGGGCG	16
(2) INFORMATION FOR SEQ ID NO:498:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:498:  GCTGAGATGG AGGGC	15
(2) INFORMATION FOR SEQ ID NO:499:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:499: GCTGAGATGG AGGG	14
(2) INFORMATION FOR SEQ ID NO:500:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:500:  GCTGAGATGG AGG	13
(2) INFORMATION FOR SEQ ID NO:501:	**

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(ii	i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  i) MOLECULE TYPE: DNA (genomic)  i) SEQUENCE DESCRIPTION: SEQ ID NO:501:  ATGG AG	12
(i (ii	FORMATION FOR SEQ ID NO:502: i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 11 base pairs    (B) TYPE: nucleic acid    (C) STRANDEDNESS: single    (D) TOPOLOGY: linear i) MOLECULE TYPE: DNA (genomic) L) SEQUENCE DESCRIPTION: SEQ ID NO:502: ATGG A	11
(i (ii	FORMATION FOR SEQ ID NO:503:  (A) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  1) MOLECULE TYPE: DNA (genomic)  2) SEQUENCE DESCRIPTION: SEQ ID NO:503:  ATGG	10
, (i	FORMATION FOR SEQ ID NO:504:  (A) LENGTH: 37 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  () MOLECULE TYPE: DNA (genomic)	
(xi CTGAGAT	.) SEQUENCE DESCRIPTION: SEQ ID NO:504: GGA GGGCGGCATG GCGGGCACAG GCTGGGC	37
(i (ii	CORMATION FOR SEQ ID NO:505:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  () MOLECULE TYPE: DNA (genomic)	
(xi CTGAGAT	) SEQUENCE DESCRIPTION: SEQ ID NO:505: GGA GGGCGGCATG GCGGGCACAG GCTGGG	36
(ii	ORMATION FOR SEQ ID NO:506:  (A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  (MOLECULE TYPE: DNA (genomic)	
	) SEQUENCE DESCRIPTION: SEQ ID NO:506: GGA GGGCGGCATG GCGGGCACAG GCTGG	35
(2) INF	ORMATION FOR SEC ID NO:507:	

(2) INFORMATION FOR SEQ ID NO:526:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 15 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:526: CTGAGATGGA GGGCG	15
(2) INFORMATION FOR SEQ ID NO:527:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:527:  CTGAGATGGA GGGC	14
(2) INFORMATION FOR SEQ ID NO:528:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:528:  CTGAGATGGA GGG	13
(2) INFORMATION FOR SEQ ID NO:529:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 12 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:529: CTGAGATGGA GG	12
(2) INFORMATION FOR SEQ ID NO:530:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 11 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:530: CTGAGATGGA G	11
(2) INFORMATION FOR SEQ ID NO:531:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:531:  CTGAGATGGA	10
(2) INFORMATION FOR SEQ ID NO:532: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 36 base pairs	

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(xi) SEQUENCE DESCRIPTION: SEQ II		
TGAGATGGAG GGCGGCATGG CGGGCACAGG  (2) INFORMATION FOR SEQ ID NO:539:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 29 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ II TGAGATGGAG GGCGGCATGG CGGGCACAG	) D NO:539:	30 29
(2) INFORMATION FOR SEQ ID NO:540:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ INTERPRETARY SEQUENCE CEGGCACA	) D NO:540:	28
(2) INFORMATION FOR SEQ ID NO:541:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 27 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ IE TGAGATGGAG GGCGGCATGG CGGGCAC	D NO:541:	27
(2) INFORMATION FOR SEQ ID NO:542:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 26 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID TGAGATGGAG GGCGGCATGG CGGGCA		26
(2) INFORMATION FOR SEQ ID NO:543:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  TGAGATGGAG GGCGGCATGG CGGGC	NO:543:	25
(2) INFORMATION FOR SEQ ID NO:544:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  TGAGATGGAG GGCGGCATGG CGGG	NO:544:	
(2) INFORMATION FOR SEQ ID NO:545:		24

(i) (ii)	RMATION FOR SEQ ID NO:558:  SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID NO:558:	10
(i) (ii) (xi)	RMATION FOR SEQ ID NO:559: SEQUENCE CHARACTERISTICS: (A) LENGTH: 35 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID NO:559: GG GCGGCATGGC GGGCACAGGC TGGGC	35
(ii) (ii)   (xi)	MATION FOR SEQ ID NO:560:  SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  MOLECULE TYPE: DNA (genomic)  SEQUENCE DESCRIPTION: SEQ ID NO:560:  G GCGGCATGGC GGGCACAGGC TGGG	34
(i) : 1 (ii) ! (ix) :	MATION FOR SEQ ID NO:561:  SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear  MOLECULE TYPE: DNA (genomic)  SEQUENCE DESCRIPTION: SEQ ID NO:561: G GCGGCATGGC GGGCACAGGC TGG	33
(i) S (ii) N (xi) S	MATION FOR SEQ ID NO:562:  SEQUENCE CHARACTERISTICS:  (A) LENGTH: 32 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  MOLECULE TYPE: DNA (genomic)  SEQUENCE DESCRIPTION: SEQ ID NO:562:  G GCGGCATGGC GGGCACAGGC TG	32
(i) S (ii) M (xi) S	MATION FOR SEQ ID NO:563: SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear MOLECULE TYPE: DNA (genomic) SEQUENCE DESCRIPTION: SEQ ID NO:563: G GCGGCATGGC GGGCACAGGC T	31
(2) INFORM (i) S	MATION FOR SEQ ID NO:564: SEQUENCE CHARACTERISTICS: (A) LENGTH: 30 base pairs	

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genom (xi) SEQUENCE DESCRIPTION: SEQUENCE GAGATGGAGG G	nic) ) ID NO:583:	. 11
(2) INFORMATION FOR SEQ ID NO:584:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQUENCE GAGATGGAGG	rs	10
(2) INFORMATION FOR SEQ ID NO:585:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 34 base pair     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genom     (xi) SEQUENCE DESCRIPTION: SEQ AGATGGAGGG CGGCATGGCG GGCACAGGCT G	ic) ID NO:585:	34
(2) INFORMATION FOR SEQ ID NO:586:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQ  AGATGGAGGG CGGCATGGCG GGCACAGGCT G	ic) ID NO:586:	33
(2) INFORMATION FOR SEQ ID NO:587:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 32 base pair:     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genom:     (xi) SEQUENCE DESCRIPTION: SEQ AGATGGAGGG CGGCATGGCG GGCACAGGCT GG	ic) ID NO:587:	32
(2) INFORMATION FOR SEQ ID NO:588:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic control of the co	ic)	31
(2) INFORMATION FOR SEQ ID NO:589:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic sequence) SEQUENCE DESCRIPTION: SEQ	c)	
AGATGGAGGG CGGCATGGCG GGCACAGGCT		30

(2) INFORMATION FOR SEQ ID NO:590:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 29 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:590: AGATGGAGGG CGGCATGGCG GGCACAGGC	29
(2) INFORMATION FOR SEQ ID NO:591:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 28 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:591: AGATGGAGGG CGGCATGGCG GGCACAGG	28
(2) INFORMATION FOR SEQ ID NO:592:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 27 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:592: AGATGGAGGG CGGCATGGCG GGCACAG	27
(2) INFORMATION FOR SEQ ID NO:593:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 26 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:593: AGATGGAGGG CGGCATGGCG GGCACA	26
(2) INFORMATION FOR SEQ ID NO:594:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 25 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:594: AGATGGAGGG CGGCATGGCG GGCAC	25
(2) INFORMATION FOR SEQ ID NO:595:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:595:  AGATGGAGGG CGGCATGGCG GGCA	24
(2) INFORMATION FOR SEQ ID NO:596: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs	

(2) INFORMATION FOR SEQ ID NO:622:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:622: GATGGAGGGC GGCATGGCGG G	21
(2) INFORMATION FOR SEQ ID NO:623:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:623:  GATGGAGGGC GGCATGGCGG	20
(2) INFORMATION FOR SEQ ID NO:624:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:624: GATGGAGGGC GGCATGGCG	19
(2) INFORMATION FOR SEQ ID NO:625:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:625: GATGGAGGGC GGCATGGC	18
(2) INFORMATION FOR SEQ ID NO:626:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:626: GATGGAGGGC GGCATGG	17
(2) INFORMATION FOR SEQ ID NO:627:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:627: GATGGAGGGC GGCATG	16
(2) INFORMATION FOR SEQ ID NO:628:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs	

(2) INFORMATION FOR SEQ ID NO:654:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:654:  ATGGAGGGCG GC	12
(2) INFORMATION FOR SEQ ID NO:655:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:655: ATGGAGGGCG G	11
(2) INFORMATION FOR SEQ ID NO:656:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:656: ATGGAGGGCG	10
(2) INFORMATION FOR SEQ ID NO:657:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 31 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:657: TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C	31
(2) INFORMATION FOR SEQ ID NO:658:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:658: TGGAGGGCGG CATGGCGGGC ACAGGCTGGG	30
(2) INFORMATION FOR SEQ ID NO:659:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 29 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:659: TGGAGGGCGG CATGGCGGGC ACAGGCTGG	29
(2) INFORMATION FOR SEQ ID NO:660: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs	

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(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genom (xi) SEQUENCE DESCRIPTION: SEQ TGGAGGGCGG CATGGCGGGC ACAGGCTG	aic)	. 28
(2) INFORMATION FOR SEQ ID NO:661:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom.  (xi) SEQUENCE DESCRIPTION: SEQ  TGGAGGGCGG CATGGCGGGC ACAGGCT	ic)	27
(2) INFORMATION FOR SEQ ID NO:662:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 26 base pair:     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genom: (xi) SEQUENCE DESCRIPTION: SEQ	ic)	26
(2) INFORMATION FOR SEQ ID NO:663:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 25 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQUENCE DESCRIPTION: SEQUENCE CATGGCGGGC ACAGG	ic)	25
(2) INFORMATION FOR SEQ ID NO:664:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 24 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ	ic)	24
(2) INFORMATION FOR SEQ ID NO:665:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi  (xi) SEQUENCE DESCRIPTION: SEQ  TGGAGGGCGG CATGGCGGGC ACA	ic)	23
(2) INFORMATION FOR SEQ ID NO:666:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 22 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi		

(2) INFORMATION FOR SEQ ID NO:686: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 23 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:686: GGAGGGCGC ATGGCGGGCA CAG

23

(2) INFORMATION FOR SEQ ID NO:687: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 base pairs(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:687:

GGAGGGCGC ATGGCGGCA CA 22

(2) INFORMATION FOR SEQ ID NO:688: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 21 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:688:

21

19

18

GGAGGGCGC ATGGCGGCA C (2) INFORMATION FOR SEQ ID NO:689:

(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 20 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:689: GGAGGGCGGC ATGGCGGCA 20

(2) INFORMATION FOR SEQ ID NO:690: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 19 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:690:

GGAGGGCGGC ATGGCGGGC

(2) INFORMATION FOR SEQ ID NO:691: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 18 base pairs (B) TYPE: nucleic acid

(C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:691: GGAGGGCGGC ATGGCGGG

(2) INFORMATION FOR SEQ ID NO:692: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 17 base pairs

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	(xi) SEQUENCE DESCRIPTION: SEQ I		
	GGGCGGC A		11
	INFORMATION FOR SEQ ID NO:699:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I	) D NO:699:	
GGA	GGGCGGC		10
	INFORMATION FOR SEQ ID NO:700:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 29 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic  (xi) SEQUENCE DESCRIPTION: SEQ INGEGEGEGE TEGGEGECA	) D NO:700:	29
(2)	INFORMATION FOR SEQ ID NO:701:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 28 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)		
GAGO	(xi) SEQUENCE DESCRIPTION: SEQ IN GCGGCA TGGCGGGCAC AGGCTGGG	O NO:701:	28
	INFORMATION FOR SEQ ID NO:702:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCGGGCA TGGCGGGCAC AGGCTGG	D NO:702:	27
	INFORMATION FOR SEQ ID NO:703:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 26 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCGGCA TGGCGGGCAC AGGCTG	) NO:703:	26
	INFORMATION FOR SEQ ID NO:704:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 25 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCGGCA TGGCGGGCAC AGGCT	NO:704:	
			25
(2)	INFORMATION FOR SEQ ID NO:705:		

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genom (xi) SEQUENCE DESCRIPTION: SEC GAGGGCGGCA TGGCGGGC	nic)	. 18
(2) INFORMATION FOR SEQ ID NO:712:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome in the second i	es es nic)	17
(2) INFORMATION FOR SEQ ID NO:713:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQ  GAGGGCGGCA TGGCGG	rs :	16
(2) INFORMATION FOR SEQ ID NO:714:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQ  GAGGGCGGCA TGGCG	s ic)	15
(2) INFORMATION FOR SEQ ID NO:715:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 14 base pair:     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genom:     (xi) SEQUENCE DESCRIPTION: SEQ GAGGGCGGCA TGGC	ic)	14
(2) INFORMATION FOR SEQ ID NO:716:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic in its sequence description: sequence descripti	ic)	13
(2) INFORMATION FOR SEQ ID NO:717:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi  (xi) SEQUENCE DESCRIPTION: SEQ  GAGGGCGGCA TG	ic)	12

11

10

28

27

26

(2) INFORMATION FOR SEQ ID NO:718: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:718:

GAGGGCGGCA T

(2) INFORMATION FOR SEQ ID NO:719:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:719:

GAGGGCGGCA

(2) INFORMATION FOR SEQ ID NO:720:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:720:

AGGGCGCAT GGCGGGCACA GGCTGGGC

(2) INFORMATION FOR SEQ ID NO:721:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:721:

AGGGCGCAT GGCGGGCACA GGCTGGG

(2) INFORMATION FOR SEQ ID NO:722:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:722:

AGGGCGCAT GGCGGCACA GGCTGG

(2) INFORMATION FOR SEQ ID NO:723:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleic acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:723:

AGGGCGCAT GGCGGCACA GGCTG

25

(2) INFORMATION FOR SEQ ID NO:724:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ I GGGCGGCATG GCGGGCACAG GCT	:)	23
(2) INFORMATION FOR SEQ ID NO:744:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ ISGGGCGCATG GCGGGCACAG GC	) D NO:744:	22
(2) INFORMATION FOR SEQ ID NO:745:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 21 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ INGEGORGE GEGGGCATG GEGGGCACAG G	) D NO:745:	21
(2) INFORMATION FOR SEQ ID NO:746:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ INGEGEGEGECATE GCGGGCACAG	) D NO:746:	20
(2) INFORMATION FOR SEQ ID NO:747:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGGCGGCATG GCGGGCACA	) D NO:747:	19
(2) INFORMATION FOR SEQ ID NO:748:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGGCGGCATG GCGGGCAC	D NO:748:	18
(2) INFORMATION FOR SEQ ID NO:749:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 17 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID	O NO:749:	
GGGCGCATG GCGGGCA		17

(2) INFORMATION FOR SEQ ID NO:750:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:750:  GGGCGGCATG GCGGGC	16
(2) INFORMATION FOR SEQ ID NO:751:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 15 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:751: GGGCGGCATG GCGGG	15
(2) INFORMATION FOR SEQ ID NO:752:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:752:  GGGCGGCATG GCGG	14
(2) INFORMATION FOR SEQ ID NO:753:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:753:  GGGCGGCATG GCG	13
(2) INFORMATION FOR SEQ ID NO:754:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:754:  GGGCGGCATG GC	12
(2) INFORMATION FOR SEQ ID NO:755:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:755:  GGGCCGGCATG G	11
(2) INFORMATION FOR SEQ ID NO:756:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs	

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(xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGCACAGG C		" 2 <u>1</u>
(2) INFORMATION FOR SEQ ID NO:763:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 20 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCCGGCATGG CGGGCACAGG	NO:763:	20
(2) INFORMATION FOR SEQ ID NO:764:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGCACAG	NO:764:	19
(2) INFORMATION FOR SEQ ID NO:765:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGCACA	NO:765:	18
(2) INFORMATION FOR SEQ ID NO:766:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGCAC	NO:766:	17
(2) INFORMATION FOR SEQ ID NO:767:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGCA	NO:767:	16
(2) INFORMATION FOR SEQ ID NO:768:    (i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 15 base pairs    (B) TYPE: nucleic acid    (C) STRANDEDNESS: single    (D) TOPOLOGY: linear    (ii) MOLECULE TYPE: DNA (genomic)    (xi) SEQUENCE DESCRIPTION: SEQ ID GGCGGCATGG CGGGC	NO:768:	15
(2) INFORMATION FOR SEQ ID NO:769:		

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genom (xi) SEQUENCE DESCRIPTION: SEQ GCGGCATGGC GGGCACAGGC TGGG	nic) ) ID NO:775:	24
(2) INFORMATION FOR SEQ ID NO:776:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 23 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome (xi) SEQUENCE DESCRIPTION: SEQUENCE GGGGCATGGC GGGCACAGGC TGG	rs :	23
(2) INFORMATION FOR SEQ ID NO:777:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 22 base pair  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom  (xi) SEQUENCE DESCRIPTION: SEQ  GCGGCATGGC GGGCACAGGC TG	s ic)	22
(2) INFORMATION FOR SEQ ID NO:778:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pair:  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genom:  (xi) SEQUENCE DESCRIPTION: SEQ  GCGGCATGGC GGGCACAGGC T	ic)	. 21
(2) INFORMATION FOR SEQ ID NO:779:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQUENCE GGGCATGGC GGGCACAGGC	ic)	20
(2) INFORMATION FOR SEQ ID NO:780:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GCGGCATGGC GGGCACAGG	ic)	19
(2) INFORMATION FOR SEQ ID NO:781:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ	.c)	18

	INFORMATION FOR SEQ ID NO:782:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:782: GCATGGC GGGCACA	17
(2)	INFORMATION FOR SEQ ID NO:783:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 16 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:783: GCATGGC GGGCAC	16
	INFORMATION FOR SEQ ID NO:784:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:784: GCATGGC GGGCA	15
	INFORMATION FOR SEQ ID NO:785:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:785: GCATGGC GGGC	14
	INFORMATION FOR SEQ ID NO:786:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:786: GCATGGC GGG	13
(2) GCG6	INFORMATION FOR SEQ ID NO:787:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:787:  GCATGGC GG	12
(2)	INFORMATION FOR SEQ ID NO:788: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 11 base pairs	

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(C) STRA (D) TOPO (ii) MOLECULE	E: nucleic acid ANDEDNESS: single DLOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEQ ID		11
(i) SEQUENCE (A) LENG (B) TYPE (C) STRA (D) TOPO (ii) MOLECULE	OR SEQ ID NO:789: CHARACTERISTICS: STH: 10 base pairs I: nucleic acid ANDEDNESS: single DLOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEQ ID	NO:789:	10
(A) LENG (B) TYPE (C) STRA (D) TOPO (ii) MOLECULE	CHARACTERISTICS: TH: 24 base pairs : nucleic acid NDEDNESS: single DLOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEO ID	NO:790:	24
(A) LENG (B) TYPE (C) STRA (D) TOPO (ii) MOLECULE	CHARACTERISTICS: TH: 23 base pairs : nucleic acid NDEDNESS: single LOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEO ID	NO:791:	23
(i) SEQUENCE (A) LENG (B) TYPE (C) STRA (D) TOPO (ii) MOLECULE	R SEQ ID NO:792: CHARACTERISTICS: TH: 22 base pairs : nucleic acid NDEDNESS: single LOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEQ ID GCT GG	NO:792:	22
(A) LENG (B) TYPE (C) STRA (D) TOPO (ii) MOLECULE	CHARACTERISTICS: TH: 21 base pairs : nucleic acid NDEDNESS: single LOGY: linear TYPE: DNA (genomic) DESCRIPTION: SEO ID	NO:793:	21
(A) LENG' (B) TYPE (C) STRAI (D) TOPO:	R SEQ ID NO:794: CHARACTERISTICS: TH: 20 base pairs : nucleic acid NDEDNESS: single LOGY: linear TYPE: DNA (genomic)		

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:794: CGGCATGGCG GGCACAGGCT	. 20
(2) INFORMATION FOR SEQ ID NO:795:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:795: CGGCATGGCG GGCACAGGC	19
(2) INFORMATION FOR SEQ ID NO:796:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 18 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:796: CGGCATGGCG GGCACAGG	18
(2) INFORMATION FOR SEQ ID NO:797:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:797: CGGCATGGCG GGCACAG	17
(2) INFORMATION FOR SEQ ID NO:798:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:798: CGGCATGGCG GGCACA	16
(2) INFORMATION FOR SEQ ID NO:799:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 15 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:799: CGGCATGGCG GGCAC	15
(2) INFORMATION FOR SEQ ID NO:800:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 14 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:800: CGGCATGGCG GGCA	14
(2) INFORMATION FOR SEQ ID NO:801:	

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( ( ( (ii) MO	QUENCE CHARACTERISTICS: A) LENGTH: 13 base pairs B) TYPE: nucleic acid C) STRANDEDNESS: single D) TOPOLOGY: linear LECULE TYPE: DNA (genomic) QUENCE DESCRIPTION: SEQ II		13
(i) SE( (/ (/ (i) (ii) MO)	FION FOR SEQ ID NO:802: QUENCE CHARACTERISTICS: A) LENGTH: 12 base pairs B) TYPE: nucleic acid C) STRANDEDNESS: single D) TOPOLOGY: linear LECULE TYPE: DNA (genomic) QUENCE DESCRIPTION: SEQ ID	) NO:802:	12
(i) SE( () (E (C (ii) MOI	TION FOR SEQ ID NO:803: QUENCE CHARACTERISTICS: A) LENGTH: 11 base pairs B) TYPE: nucleic acid C) STRANDEDNESS: single D) TOPOLOGY: linear ECULE TYPE: DNA (genomic) QUENCE DESCRIPTION: SEQ ID	NO:803:	11
(i) SEC (A (E (C (C (ii) MOI	PION FOR SEQ ID NO:804: DUENCE CHARACTERISTICS: DUENGTH: 10 base pairs DUENCE TYPE: nucleic acid DUENCE STRANDEDNESS: single DUENCE TYPE: DNA (genomic) DUENCE DESCRIPTION: SEQ ID	NO:804:	10
(i) SEQ (A (B (C (D (ii) MOL (xi) SEQ	ION FOR SEQ ID NO:805: UENCE CHARACTERISTICS: ) LENGTH: 23 base pairs ) TYPE: nucleic acid ) STRANDEDNESS: single ) TOPOLOGY: linear ECULE TYPE: DNA (genomic) UENCE DESCRIPTION: SEQ ID CACAGGCTG GGC	NO:805:	23
(i) SEQ (A (B (C (D (ii) MOL	ION FOR SEQ ID NO:806: UENCE CHARACTERISTICS: ) LENGTH: 22 base pairs ) TYPE: nucleic acid ) STRANDEDNESS: single ) TOPOLOGY: linear ECULE TYPE: DNA (genomic) UENCE DESCRIPTION: SEQ ID CACAGGCTG GG	NO:806:	22
(2) INFORMAT (i) SEQ (A (B	ION FOR SEQ ID NO:807: UENCE CHARACTERISTICS: ) LENGTH: 21 base pairs ) TYPE: nucleic acid ) STRANDEDNESS: single		

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GGCATGGCGG GCACAGGCTG G	ic)	. 21
(2) INFORMATION FOR SEQ ID NO:308:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomical) SEQUENCE DESCRIPTION: SEQUENCE GGCATGGCGG GCACAGGCTG	ic)	20
(2) INFORMATION FOR SEQ ID NO:809:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 19 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GGCATGGCGG GCACAGGCT	.c)	. 19
(2) INFORMATION FOR SEQ ID NO:810:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi  (xi) SEQUENCE DESCRIPTION: SEQ  GGCATGGCGG GCACAGGC	.c)	18
(2) INFORMATION FOR SEQ ID NO:811:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQUENCE GGCATGGCGG GCACAGG	c)	17
(2) INFORMATION FOR SEQ ID NO:812:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ GGCATGGCGG GCACAG	c)	16
(2) INFORMATION FOR SEQ ID NO:813:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 15 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic (xi) SEQUENCE DESCRIPTION: SEQ INGCATGGCGG GCACA		15

(2) INFORMATION FOR SEQ ID NO:814:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:814:  GGCATGGCGG GCAC	14
(2) INFORMATION FOR SEQ ID NO:815:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:815: GGCATGGCGG GCA	13
(2) INFORMATION FOR SEQ ID NO:816:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 12 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:816: GGCATGGCGG GC	12
(2) INFORMATION FOR SEQ ID NO:817:         (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear         (ii) MOLECULE TYPE: DNA (genomic)         (xi) SEQUENCE DESCRIPTION: SEQ ID NO:817: GGCATGGCGG G	11
(2) INFORMATION FOR SEQ ID NO:818:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 10 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:818: GGCATGGCGG	10
(2) INFORMATION FOR SEQ ID NO:819:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 22 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:819: GCATGGCGGG CACAGGCTGG GC	22
(2) INFORMATION FOR SEQ ID NO:820:    (i) SEQUENCE CHARACTERISTICS:    (A) LENGTH: 21 base pairs	

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(xi) SEQUENCE DESCRIPTION: SEQ IS GCATGGCGGG CACAG		15
(2) INFORMATION FOR SEQ ID NO:827:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ INGESTATEMENT (CALLE TYPE)	) D NO:827:	14
(2) INFORMATION FOR SEQ ID NO:828:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCATGGCGGG CAC	D NO:828:	13
(2) INFORMATION FOR SEQ ID NO:829:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCATGGCGGG CA	NO:829:	12
(2) INFORMATION FOR SEQ ID NO:830:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GCATGGCGGG C	NO:830:	. 11
(2) INFORMATION FOR SEQ ID NO:831:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GCATGGCGGG	NO:831:	10
(2) INFORMATION FOR SEQ ID NO:832:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 21 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  CATGGCGGGC ACAGGCTGGG C	NO:832:	21
(2) INFORMATION FOR SEC ID NO. 833.		<u> </u>

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(D) TOPOLOGY: linear	133	
(ii) MOLECULE TYPE: DNA (gen (xi) SEQUENCE DESCRIPTION: S CATGGCGGGC ACAG	omic) EQ ID NO:839:	14
(2) INFORMATION FOR SEQ ID NO:84  (i) SEQUENCE CHARACTERISTIC  (A) LENGTH: 13 base pa  (B) TYPE: nucleic acid  (C) STRANDEDNESS: sing  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (general)  (xi) SEQUENCE DESCRIPTION: STATESTICATION: STA	S: irs le omic)	13
(2) INFORMATION FOR SEQ ID NO:841  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 12 base par  (B) TYPE: nucleic acid  (C) STRANDEDNESS: sings  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome)  (xi) SEQUENCE DESCRIPTION: SECATGGCGGGC AC	S: irs le omic)	12
(2) INFORMATION FOR SEQ ID NO:842  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 11 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome)  (xi) SEQUENCE DESCRIPTION: SECATGGCGGGC A	S: irs le omic)	11
(2) INFORMATION FOR SEQ ID NO:843 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 10 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (gence) (xi) SEQUENCE DESCRIPTION: SECATGGCGGGC	3: irs Le omic)	
(2) INFORMATION FOR SEQ ID NO:844  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 20 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (geno  (xi) SEQUENCE DESCRIPTION: SE  ATGGCGGGCA CAGGCTGGGC	s: rs .e omic)	20
(2) INFORMATION FOR SEQ ID NO:845 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 19 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (geno (xi) SEQUENCE DESCRIPTION: SE ATGGCGGGCA CAGGCTGGG	rs e emic)	10
<del> </del>		19

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(2) INFORMATION FOR SEQ ID NO:846:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 18 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:846:  ATGGCGGGCA CAGGCTGG	18
(2) INFORMATION FOR SEQ ID NO:847:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:847: ATGGCGGGCA CAGGCTG	17
(2) INFORMATION FOR SEQ ID NO:848:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:848: ATGGCGGGCA CAGGCT	16
(2) INFORMATION FOR SEQ ID NO:849:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 15 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:849: ATGGCGGGCA CAGGC	15
(2) INFORMATION FOR SEQ ID NO:850:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 14 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:850: ATGGCGGGCA CAGG	14
(2) INFORMATION FOR SEQ ID NO:851:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:851: ATGGCGGGCA CAG	13
(2) INFORMATION FOR SEQ ID NO:852: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 12 base pairs	

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(xi) SEQUENCE DESCRIPTION: TGGCGGGCAC AGGCTG		. 16
(2) INFORMATION FOR SEQ ID NO:8  (i) SEQUENCE CHARACTERISTI  (A) LENGTH: 15 base p  (B) TYPE: nucleic aci  (C) STRANDEDNESS: sin  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (ge  (xi) SEQUENCE DESCRIPTION: TGGCGGGCAC AGGCT	CS: pairs d gle nomic)	15
(2) INFORMATION FOR SEQ ID NO:8  (i) SEQUENCE CHARACTERISTIC  (A) LENGTH: 14 base position of the content of th	CS: airs d gle nomic)	14
(2) INFORMATION FOR SEQ ID NO:80 (i) SEQUENCE CHARACTERISTIC (A) LENGTH: 13 base pa (B) TYPE: nucleic acid (C) STRANDEDNESS: sing (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (gen (xi) SEQUENCE DESCRIPTION: STGGCGGGCAC AGG	CS: airs d gle nomic)	13
(2) INFORMATION FOR SEQ ID NO:86  (i) SEQUENCE CHARACTERISTIC  (A) LENGTH: 12 base pa  (B) TYPE: nucleic acid  (C) STRANDEDNESS: sing  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (ger  (xi) SEQUENCE DESCRIPTION: ST	CS: airs d gle nomic)	12
(2) INFORMATION FOR SEQ ID NO:86  (i) SEQUENCE CHARACTERISTIC  (A) LENGTH: 11 base pa  (B) TYPE: nucleic acid  (C) STRANDEDNESS: sing  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (gen  (xi) SEQUENCE DESCRIPTION: STAGGCGGGCAC A	CS: airs d gle nomic)	11
(2) INFORMATION FOR SEQ ID NO:86  (i) SEQUENCE CHARACTERISTIC  (A) LENGTH: 10 base pa  (B) TYPE: nucleic acid  (C) STRANDEDNESS: sing  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (gen  (xi) SEQUENCE DESCRIPTION: S TGGCGGGCAC	CS: airs d gle gle nomic) GEQ ID NO:864:	10
(2) INFORMATION FOR SEQ ID NO:86	55:	

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GGCGGGCACA GG	.c) ID NO:871:	
(2) INFORMATION FOR SEQ ID NO:872:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 11 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic in its sequence description: SEQ)  GGCGGGCACA G	.c)	11
(2) INFORMATION FOR SEQ ID NO:873:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 10 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi  (xi) SEQUENCE DESCRIPTION: SEQ  GGCGGGCACA	.c)	10
(2) INFORMATION FOR SEQ ID NO:874:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 17 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GCGGGCACAG GCTGGGC	c)	17
(2) INFORMATION FOR SEQ ID NO:875:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi     (xi) SEQUENCE DESCRIPTION: SEQ GCGGGCACAG GCTGGG	c)	16
(2) INFORMATION FOR SEQ ID NO:876:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 15 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomi     (xi) SEQUENCE DESCRIPTION: SEQ GCGGGCACAG GCTGG	c)	15
(2) INFORMATION FOR SEQ ID NO:877:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomi (xi) SEQUENCE DESCRIPTION: SEQ GCGGGCACAG GCTG	c)	14

(2) INFORMATION FOR SEQ ID NO:878:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:878:  GCGGGCACAG GCT	13
(2) INFORMATION FOR SEQ ID NO:879:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 12 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:879: GCGGGCACAG GC	12
(2) INFORMATION FOR SEQ ID NO:880:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 11 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:880: GCGGGCACAG G	11
(2) INFORMATION FOR SEQ ID NO:881:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:881: GCGGGCACAG	10
(2) INFORMATION FOR SEQ ID NO:882:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 16 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:882: CGGGCACAGG CTGGGC	16
(2) INFORMATION FOR SEQ ID NO:883:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 15 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:883: CGGGCACAGG CTGGG	15
(2) INFORMATION FOR SEQ ID NO:884:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs	

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(with Chourney programment of the	141	
(xi) SEQUENCE DESCRIPTION: SEQ ID GGGCACAGGC TGGG	NO:890:	14
(2) INFORMATION FOR SEQ ID NO:891:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 13 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGGCACAGGC TGG	NO:891:	13
(2) INFORMATION FOR SEQ ID NO:892:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 12 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID  GGGCACAGGC TG	NO:892:	12
(2) INFORMATION FOR SEQ ID NO:893:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 11 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGGCACAGGC T	NO:893:	
(2) INFORMATION FOR SEQ ID NO:894:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 10 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGGCACAGGC	NO:894:	11
(2) INFORMATION FOR SEQ ID NO:895:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 14 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID GGCACAGGCT GGGC	NO:895:	14
(2) INFORMATION FOR SEQ ID NO:896:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 13 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID 19 GGCACAGGCT GGG	NO:896:	
		13
(2) INFORMATION FOR SEQ ID NO:897:		

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(A) LENGT (B) TYPE: (C) STRAN (D) TOPOL (ii) MOLECULE T	HARACTERISTICS: CH: 12 base pairs nucleic acid EDEDNESS: single OGY: linear YPE: DNA (genomic) ESCRIPTION: SEQ ID NO:897:	12
(A) LENGT (B) TYPE: (C) STRAN (D) TOPOL (ii) MOLECULE T	SEQ ID NO:898: HARACTERISTICS: H: 11 base pairs nucleic acid DEDNESS: single OGY: linear YPE: DNA (genomic) ESCRIPTION: SEQ ID NO:898:	11
(A) LENGTI (B) TYPE: (C) STRANI (D) TOPOLO (ii) MOLECULE TY	SEQ ID NO:899: HARACTERISTICS: H: 10 base pairs nucleic acid DEDNESS: single OGY: linear YPE: DNA (genomic) ESCRIPTION: SEQ ID NO:899:	10
(A) LENGTH (B) TYPE: (C) STRANH (D) TOPOLO (ii) MOLECULE TY	SEQ ID NO:900: HARACTERISTICS: H: 13 base pairs nucleic acid DEDNESS: single DGY: linear YPE: DNA (genomic) ESCRIPTION: SEQ ID NO:900:	13
(B) TYPE: (C) STRAND (D) TOPOLO (ii) MOLECULE TY	SEQ ID NO:901: HARACTERISTICS: H: 12 base pairs nucleic acid DEDNESS: single DGY: linear YPE: DNA (genomic) ESCRIPTION: SEQ ID NO:901:	12
(B) TYPE: (C) STRAND (D) TOPOLO (ii) MOLECULE TY		11
(B) TYPE:		

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(D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomial) SEQUENCE DESCRIPTION: SEGCACAGGCTG	omic)	10
(2) INFORMATION FOR SEQ ID NO: 90% (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 12 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomical (xi) SEQUENCE DESCRIPTION: SECACAGGCTGG GC	S: irs Le omic)	12
(2) INFORMATION FOR SEQ ID NO: 905  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 11 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genome)  (xi) SEQUENCE DESCRIPTION: SECACAGGCTGG G	s: .rs .e omic)	. 11
(2) INFORMATION FOR SEQ ID NO:906 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 10 base pai (B) TYPE: nucleic acid (C) STRANDEDNESS: singl (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (geno (xi) SEQUENCE DESCRIPTION: SE	e mic)	10
(2) INFORMATION FOR SEQ ID NO:907  (i) SEQUENCE CHARACTERISTICS  (A) LENGTH: 11 base pai  (B) TYPE: nucleic acid  (C) STRANDEDNESS: singl  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomical sequence)  (xi) SEQUENCE DESCRIPTION: SECUENCE CONTROL C	: rs e mic)	11
(2) INFORMATION FOR SEQ ID NO:908 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 10 base pair (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome in the second in the se	: rs e mic)	10
(2) INFORMATION FOR SEQ ID NO:909 (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 10 base pair (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genome in the second in the se	: rs e nic)	10

(2) INFORMATION FOR SEQ ID NO:910: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 51 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:910: GGCGGCCTGG AAAGCTGAGA TGGAGGGCGG CATGGCGGGC ACAGGCTGGG C 51 (2) INFORMATION FOR SEQ ID NO:911: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 50 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:911: GCGGCCTGGA AAGCTGAGAT GGAGGGCGGC ATGGCGGGCA CAGGCTGGGC 50 (2) INFORMATION FOR SEQ ID NO:912: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 49 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:912: CGGCCTGGAA AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC 49 (2) INFORMATION FOR SEQ ID NO:913: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 48 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:913: GGCCTGGAAA GCTGAGATGG AGGGCGGCAT GGCGGGCACA GGCTGGGC 48 (2) INFORMATION FOR SEQ ID NO:914: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 47 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:914: GCCTGGAAAG CTGAGATGGA GGGCGGCATG GCGGGCACAG GCTGGGC 47 (2) INFORMATION FOR SEQ ID NO:915: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 46 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:915: CCTGGAAAGC TGAGATGGAG GGCGGCATGG CGGGCACAGG CTGGGC 46 (2) INFORMATION FOR SEQ ID NO:916: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 45 base pairs (B) TYPE: nucleic acid

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146 AGCTGAGATG GAGGGCGGCA TGGCGGGCAC AGGCTGGGC	
AGCIGAGE GAGGGGGCA IGGCGGGCAC AGGCIGGGC	39
(2) INFORMATION FOR SEQ ID NO:923:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 38 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear	
<pre>(ii) MOLECULE TYPE: DNA (genomic)   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:923: GCTGAGATGG AGGGCGCAT GGCGGGCACA GGCTGGGC (2) INFORMATION FOR SEQ ID NO:924:    (i) SEQUENCE CHARACTERISTICS:        (A) LENGTH: 37 base pairs        (B) TYPE: nucleic acid        (C) STRANDEDNESS: single        (D) TOPOLOGY: linear</pre>	38
(ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:924: CTGAGATGGA GGGCGCATG GCGGGCACAG GCTGGGC	37
(2) INFORMATION FOR SEQ ID NO:925:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:925: TGAGATGGAG GGCGCATGG CGGGCACAGG CTGGGC	36
(2) INFORMATION FOR SEQ ID NO:926:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 35 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:926: GAGATGGAGG GCGGCATGGC GGGCACAGGC TGGGC	35
(2) INFORMATION FOR SEQ ID NO:927:     (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 34 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:927: AGATGGAGGG CGGCATGGCG GGCACAGGCT GGGC	34
(2) INFORMATION FOR SEQ ID NO:928:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 33 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:928:  GATGGAGGGC GGCATGGCGG GCACAGGCTG GGC	33
<ul><li>(2) INFORMATION FOR SEQ ID NO:929:</li><li>(i) SEQUENCE CHARACTERISTICS:</li><li>(A) LENGTH: 32 base pairs</li></ul>	

		<pre>INFORMATION FOR SEQ ID NO:955:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 29 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single         (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:955: GGC CGT GCG GCT CTG TCG CTC CCG GT</pre>	29
		<pre>INFORMATION FOR SEQ ID NO:956:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 20 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single             (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:956: CCG CCC TCC GGG GGG TC</pre>	20
	(2)	<pre>INFORMATION FOR SEQ ID NO:957:    (i) SEQUENCE CHARACTERISTICS:         (A) LENGTH: 18 base pairs         (B) TYPE: nucleic acid         (C) STRANDEDNESS: single             (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:957: TGC CGT TGG CTG CCC</pre>	18
		INFORMATION FOR SEQ ID NO:958:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 17 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:958:  CTG CGG GTC GCC GG	17
		INFORMATION FOR SEQ ID NO:959:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:959: TGG GCT TGT GGC	15
		INFORMATION FOR SEQ ID NO:960:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 15 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:960:  CTC TCT TCT GGG	15
(	2)	INFORMATION FOR SEQ ID NO:961:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 14 base pairs	

(2) INFORMATION FOR SEQ ID NO:974:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 20 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:974:  GCC TGG GGC TCC CTT CTC	20
(2) INFORMATION FOR SEQ ID NO:975:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 19 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:975:  GCC CTT CTT GCT GGG CCT C	19
(2) INFORMATION FOR SEQ ID NO:976:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 25 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:976: TGC TGC TGC TGG TGC TGT GGC CCC C	25
(2) INFORMATION FOR SEQ ID NO:977:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:978:  GTACACCGAGGAGCCCATGATGGGCATGCCACAGACGACAGGC	43
(2) INFORMATION FOR SEQ ID NO:978:  (i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 43 base pairs  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: DNA (genomic)  (xi) SEQUENCE DESCRIPTION: SEQ ID NO:978:  GTBCBCCGBGGGGCCCBTGBTGGGCCBCBGBCGBCCBGGC	43
(2) INFORMATION FOR SEQ ID NO:979:     (i) SEQUENCE CHARACTERISTICS:     (A) LENGTH: 29 base pairs     (B) TYPE: nucleic acid     (C) STRANDEDNESS: single     (D) TOPOLOGY: linear     (ii) MOLECULE TYPE: DNA (genomic)     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:979: GGC GCC GTG CCG CGT CTT GGT GGC GGC GG	29
(2) INFORMATION FOR SEQ ID NO:980: (i) SEQUENCE CHARACTERISTICS:	

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(2) INFORMATION FOR SEQ ID NO:993:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 14 base pairs
            (B) TYPE: nucleic acid
            (C) STRANDEDNESS: single
            (D) TOPOLOGY: linear
     (ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:993:
TTT CTT CTG TTC CC
                                                                                      14
(2) INFORMATION FOR SEQ ID NO:994:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 18 base pairs
            (B) TYPE: nucleic acid
     (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:994:
CCC TTT TCT GGT GGG GTG
                                                                                      18
(2) INFORMATION FOR SEQ ID NO:995:
      (i) SEQUENCE CHARACTERISTICS:
            (A) LENGTH: 15 base pairs
            (B) TYPE: nucleic acid
    (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: DNA (genomic)
     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:995:
GTG CTG TTG TTG GGC
                                                                                      15
(2) INFORMATION FOR SEQ ID NO:996:
      (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 14 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:996:
TTT CTT CTG TTC CC
                                                                                      14
(2) INFORMATION FOR SEQ ID NO:997:
     (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 21 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
           (D) TOPOLOGY: linear
    (ii) MOLECULE TYPE: DNA (genomic)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:997:
CTC GTC GCC GTC GCC GGG
                                                                                   21
(2) INFORMATION FOR SEQ ID NO:998:
     (i) SEQUENCE CHARACTERISTICS:
           (A) LENGTH: 20 base pairs
           (B) TYPE: nucleic acid
           (C) STRANDEDNESS: single
    (D) TOPOLOGY: linear (ii) MOLECULE TYPE: DNA (genomic)
    (xi) SEQUENCE DESCRIPTION: SEQ ID NO:998:
GGG TGG TGC TAT TGT CGG GC
                                                                                      20
(2) INFORMATION FOR SEQ ID NO:999:
     (i) SEQUENCE CHARACTERISTICS:
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WO 99/63938

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/12775

IPC(6) :A61K 48/0 US CL :536/23.1, 2 According to Internation	ION OF SUBJECT MATTER 10; C07H 21/04, 21/00; C12N 5/00, 15/ 23.2, 24.5, 24.3; 435/91.1, 375, 6; 514 101 Patent Classification (IPC) or to both	1/44			
B. FIELDS SEARC					
Minimum documentatio	n searched (classification system followers	ed by classification symbols)			
	3.2, 24.5, 24.3; 435/91.1, 375, 6; 514/				
		e extent that such documents are included	in the fields searched		
USPTO NPL, Proque					
Electronic data base con	nsulted during the international search (r	name of data base and, where practicable	e, search terms used)		
Please See Extra Shee	et.				
C. DOCUMENTS	CONSIDERED TO BE RELEVANT				
Category* Citation	n of document, with indication, where a	ppropriate, of the relevant passages	Relevant to claim No.		
	40266 A1 (EAST CAROLINA age 7, lines 14-21.	UNIVERSITY) 19 December	1-79		
	WO 98/23294 A1 (EAST CAROLINA UNIVERSITY) 04 June 1-79 1998, page 1, lines 9-15.				
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Further document	ts are listed in the continuation of Box (	C. See patent family annex.			
	of cited documents:	*T* later document published after the inte	mational filing date or priority		
	the general state of the art which is not considered	date and not in conflict with the appli the principle or theory underlying the	cation but cited to understand		
	ublished on or after the international filing date	"X" document of particular relevance; the considered novel or cannot be consider	claimed invention cannot be		
cited to establish t	tay throw doubts on priority claim(s) or which is the publication date of another citation or other	when the document is taken alone	•		
special reason (as a	specified) to an oral disclosure, use, exhibition or other	"Y" document of particular relevance; the considered to involve an inventive combined with one or more other such	step when the document is		
means	d prior to the international filing date but later than	being obvious to a person skilled in th	no art		
the priority date ch	nim ed		•		
	letion of the international search	Date of mailing of the international sea	rch report		
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Facsimile No. (703) 3	05-3230	Telephone No. (703) 308-0196	`		

## INTERNATIONAL SEARCH REPORT

International application No. PCT/US99/12775

B. FIELDS SEARCHED  Electronic data bases consulted (Name of data base and where practicable terms used):						
APS, STN-Caplus, Inpadoc, Dialog-Medline, Biotech-Biobus cluster search terms: antisense, ribozyme, aptamer, triplex, adenosine receptor, cardiopulmonary and renal failure or disease or disorder, endotoxin release, acute respiratory distress syndrome or ARDS, ischemia						
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